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The Hydraulic Lung

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ABSTRACT

A Hydraulic Lung has been designed and constructed. The Hydraulic Lung can inhale through a Dry Powder Inhaler (DPI) with a pre-determined level of inspiratory effort, and the characteristics of the inhalation profile generated, such as the peak pressure drop, peak flow rate and the flow acceleration are determined by the resistivity of the inhaler. The Hydraulic Lung has been used to explore the relationship between the level of inspiratory effort, the DPI resistivity and the resultant profile characteristics.

A simple empirical equation has been found to describe the peak pressure drop achieved for any given level of inspiratory effort and device resistivity. This equation can be adapted to provide the equivalent peak inspiratory flow rate. A second simple empirical equation was found to describe the flow acceleration rate achieved under defined conditions of inspiratory effort and device resistivity. A clinical study has been performed to generate equivalent human inhalation data. A comparison between the relationships derived from the Hydraulic Lung data and the human inhalation data has demonstrated the validity of the key equation for pressure drop as a tool for predicting human inhalation characteristics. The equation for flow acceleration rate was found to underestimate the flow accelerations achieved by human volunteers, but with slight modification could be used for this purpose.

Correlations were established between the findings from this study and the work of earlier researchers in this area, which was based on clinical data alone.

The Hydraulic Lung was also used as a practical tool for the evaluation of DPI performance *in-vitro*, including the behaviour of devices with variable resistivity which cannot easily be assessed using either standard pumps or sophisticated apparatus such as the Electronic Lung.

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Dedicated to Susan, James and Laura

TABLE OF CONTENTS

List of Figures

List of Tables

1. INTRODUCTION

1.1. Asthma and its treatment

Most of the world's ancient cultures of which we have records have recognised the complaint we know as 'asthma'. The word 'asthma' itself, from the Greek term meaning 'panting', has been in use for at least 2500 years. The disease is characterised by difficulty in breathing, wheezing and 'tightness' in the chest. Innumerable remedies have been tried across the span of centuries, but the most successful of these have involved the inhalation of smoke or 'medicated vapours'.

The inhaled route of administration allows the active ingredient of the medication (if one is present) to deposit directly onto the central and alveolar regions of the lungs, the site of the disease. This allows rapidity of action and the maximum therapeutic benefit and consequently the inhaled route remains the most successful and popular means of treatment for asthma today.

An effective medicine requires both an effective drug and an efficient means of delivery. In the treatment of asthma, highly effective drugs appeared in the early 1950s (Keeley, 1997). Asthma drugs fell into two major classes; beta-agonists such as Salbutamol, which provide a rapid relief of the symptoms, and corticosteroids such as Beclomethasone dipropionate, which act as preventatives. These drugs were initially administered by the oral route. The oral route of treatment has two major disadvantages in the treatment of asthma where the target of the therapy is the lungs: The onset of action of the drug is relatively slow since the drug has to be absorbed through the digestive

system and travel through the circulatory system before it can reach the lungs. This is a particular disadvantage for beta-agonists which are likely to be used during acute attacks. The second disadvantage is the large total dose required to deliver a relatively small dose to the lungs. This is a particular disadvantage for the corticosteroids where regular large doses can result in significant side effects.

Administration of the drugs by inhalation could only be achieved by use of a nebuliser, typically a large piece of equipment, situated in a hospital or in the home.

1.2. Pressurised Metered Dose Inhalers

The breakthrough in delivery of these drugs was the development of the pressurised metered dose inhaler (MDI), which first appeared in 1956 (Fink, 2000). The first MDIs contained a solution of drug in a propellant/alcohol mixture. The alcohol aided solubilisation of the drug and the propellant, a volatile chlorofluorocarbon mixture, maintained the pressure within the inhaler can. Unlike a normal aerosol can, such as a hair spray, which has a continuous spray valve, the inhaler was fitted with a fixed volume metering valve. The metering valve, when activated by pressing the valve stem, would transfer a small volume of the formulation from the pressurised interior of the can to the outside. The propellant mixture would then expand rapidly through a narrow bore nozzle in the actuator forming a cloud of aerosolised droplets which could be inhaled. The droplets would begin to evaporate immediately, with the result that both solid particles and droplets could deposit within the lungs. Alternative formulations, which contained the drug as a suspension in the propellant mixture followed in 1957. The small size of MDIs combined with their effectiveness, low cost and multi-dose capacity has resulted in their huge popularity; with over 440 million MDIs a year being produced by 1998 (Fink,

2000). MDIs are the second most common form of medication of any type; the first being the tablet.

1.3. Dry Powder Inhalers

1.3.1. The history of Dry Powder Inhalers

The Dry Powder Inhaler (DPI) was developed as an alternative to the MDI, originally to overcome the problem of patient coordination. MDIs are typically actuated by hand; requiring the patient to inhale the aerosolised cloud as it is generated for satisfactory dosing to occur. This manoeuvre is difficult for some patients to achieve. By contrast, DPIs are typically actuated by the patient's own inhalation, thus ensuring good co-ordination. The first modern dry powder inhaler was described in 1949 (Fields, 1949) though the first popular dry powder device was the Spinhaler (Bell, 1971). In this device a hard gelatin capsule containing the powder formulation is placed on a rotor mechanism, such that air drawn through the device causes the rotor and capsule to spin rapidly. Prior to operation, the capsule is pierced by two needles, so that the spinning action releases powder from the capsule into the airstream. The powder formulation consisted of a blend of micronised drug (particles approximately 3 microns in diameter) with coarser lactose acting as an excipient to improve the flow properties of the formulation.

A drug-lactose formulation contained within a capsule formed the basis of other DPI products such as the Rotahaler (Over and Dah, 1985). The key disadvantage of these DPI products in comparison to MDIs is convenience to the patient. A typical MDI contains two hundred doses of the drug while capsule-based DPIs have to be loaded with a new

capsule for each dose. This disadvantage led to the development of multi-dose DPIs such as the Diskhaler (Sumby *et al*, 1993), the Turbuhaler (Wetterlin, 1988) and, more recently, the Accuhaler/Diskus (Brindley *et al*, 1995).

1.4. Advantages and disadvantages of DPIs and MDIs

Like the Spinhaler, currently marketed DPI products are generally actuated by the patients inhalation and therefore do not require the patient to coordinate inhalation and actuation.

It should be noted that some manufacturers of MDIs have addressed this problem by developing either mechanisms which automatically actuate the inhaler when the patient inhales, such as the Easibreathe (Farmer *et al*, 2000), or through the use of spacer devices such as the Volumatic (Selroos and Halme, 1991) which hold the aerosolised dose in a chamber for up to a minute after actuation, allowing the patient to inhale without the need for coordination.

An important further incentive in the development of DPIs was the increasing environmental concern over the use of ozone depleting chemicals such as chlorofluorocarbons (CFCs). These were widely used as refrigerants, in the production of plastics and as propellants in aerosols. In relatively small quantities (less than 1% of world usage) CFCs were also used as propellants in MDIs for the treatment of asthma. The Montreal Protocol, drafted by the United Nations Environmental Programme in 1987, resulted in the end of CFC production for non-essential uses in 1996 (in the developed world). Although medical applications such as MDIs were given exemption

from the ban, the manufacture of CFCs on a large scale ceased and manufacturers were forced to seek alternative, environmentally-friendly propellants. Reformulation of MDI products with alternative propellants proved difficult, with only one product launched using non-CFC propellants by the end of 1995, despite almost a decade of development.

1.5. Current trends in the market for inhaled products

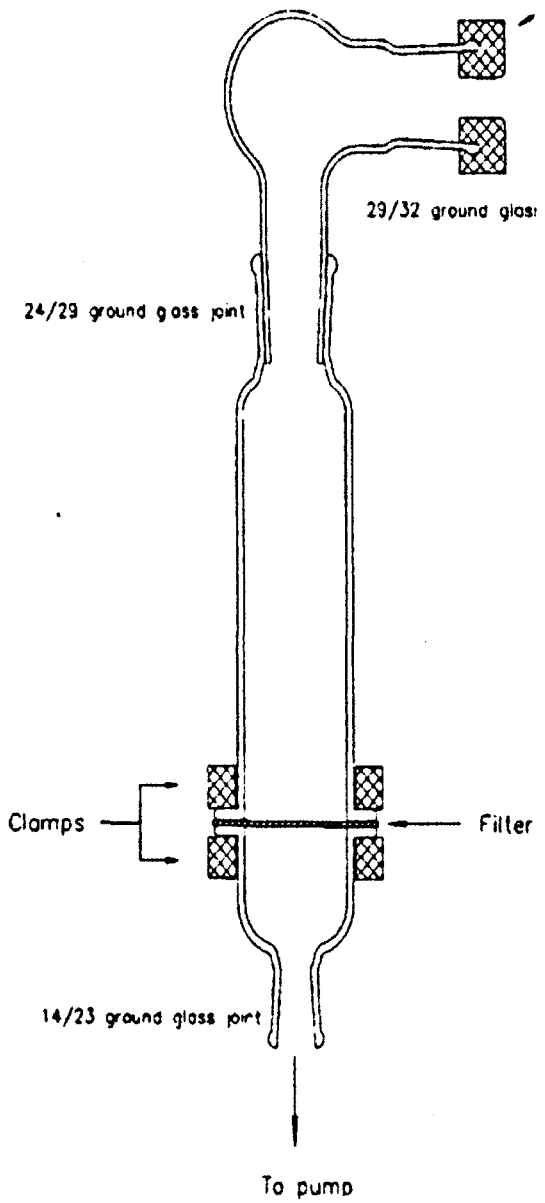
The difficulty and cost of reformulating MDI products increased the incentive to develop new, and better DPIs to capture a greater share of the MDI market and bring new products to market more cheaply. Consequently the number of patents registered for DPI devices increased from approximately 5 per year in the late 1980s to approximately 25 per year a decade later.

1.6. *In-vitro* testing of DPIs

In-vitro testing of DPIs has evolved over almost forty years since they first appeared. The first DPI products were based on capsules filled with the powder formulation and therefore the tests typically applied were those which had been used for oral capsule products, such as bulk drug content or drug content uniformity. These tests gave an indication of the total quantity of drug potentially available to the patient from each dose. However, in use some of the formulation would remain in the capsule and some would adhere to the device itself after inhalation. This could represent a significant portion of the theoretically available drug and therefore the total drug content would always overestimate the dose received by the patient. Tests were therefore devised to determine the dose that was emitted from the device. Emitted dose testing was already established

for MDIs, but since the energy required to aerosolise the dose from a MDI is provided by the rapid expansion of the propellants, the air flow rate through the apparatus capturing the dose was not important, provided it was sufficient to prevent the escape (or 'blowback') of any material. In the case of a typical DPI, the energy required to aerosolise the dose must come from the patient's inhalation. Bell (1971) chose 60 litres.minute^{-1} as the flow rate to test dose emptying of the Spinhaler, probably based on the flow rates achieved through a test device by volunteers. This flow rate was subsequently adopted for the testing of many other DPIs and became incorporated in test monographs (British Pharmacopoeia, 1993; US Pharmacopoeial Convention, 1994). It was found to be clinically relevant for other DPIs (Engel, 1990; Spiro, 1992) either as a minimum flow rate or a mean flow rate. A typical emitted dose collection apparatus is shown in Figure 1.1.

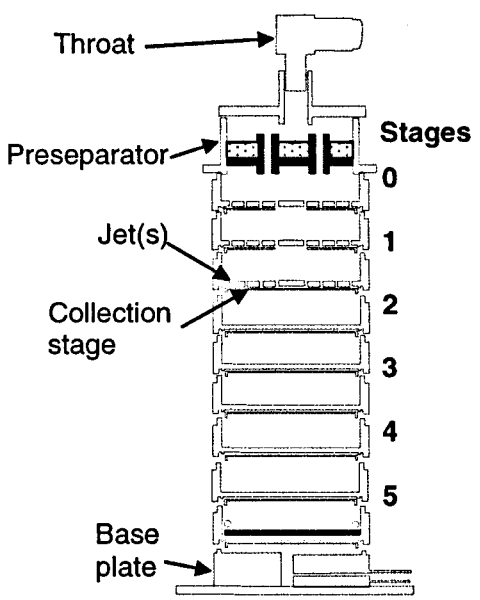
Figure 1.1 A typical emitted dose apparatus



It is important for successful treatment that an inhaler should deliver a consistent quantity of drug from dose to dose. It is equally important for drug delivery to the lungs that the size distribution of the emitted drug is controlled, and the proportion of the drug that is small enough to be respirable (typically particles less than 6 microns in diameter) is consistent. This size distribution is generally determined by an impaction or impingement

technique (May, 1966; May, 1945; Halworth, 1987) The dose is drawn out of the inhaler and passes through one or more sets of restrictions, or jets. As the particles pass through a jet, those which have sufficient momentum will strike a collection surface below the jet and be captured. Smaller particles with less momentum will be able to follow the airflow and remain in the airstream. Successive jets get smaller, resulting in faster air velocity and the capture of increasingly small particles. A common impaction apparatus used for this purpose, the Anderson Cascade Impactor (Figure 1.2), has seven collection stages, each capturing particles within a narrow size range.

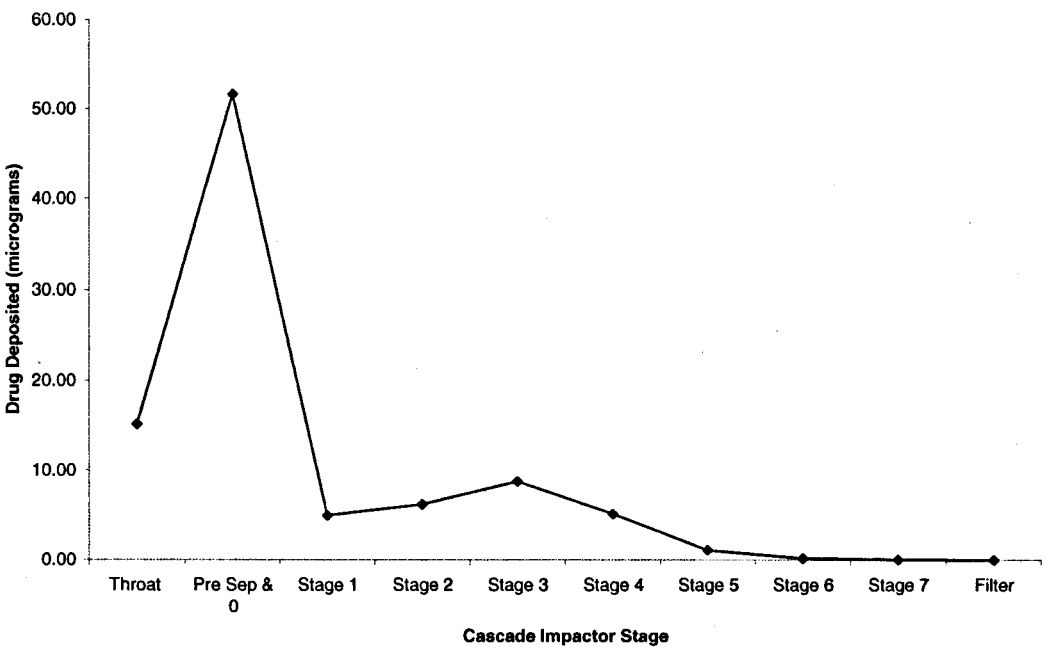
Figure 1.2 The Andersen Cascade Impactor



The coarsest, non-respirable particles can be removed by a pre-separator preceding the collection stages, and extremely fine material is collected on a filter at the end of the apparatus. The quantity of drug captured on each stage of the impactor can be determined so that a profile of the drug size distribution can be achieved (Figure 1.3). The size of the

material collected on each impaction plate is determined by the flow rate of the air passing through the relevant jets, so for accurate sizing the flow rate must also be accurate and as constant as possible.

Figure 1.3 Example of distribution of drug within a Cascade Impactor



Bell (1971) used an impinger apparatus to determine the particle size distribution of the drug emitted from the Spinhaler, and as for the determination of the dose emptying, he used a flow rate of 60 litres.minute^{-1}.

This flow rate was also adopted thereafter for many similar tests of drug particle size delivered from DPIs. Bell achieved the flow through his test apparatus using a vacuum pump. The vacuum pump would be pre-set to pull a flow rate of 60 litres.minute^{-1} and the pump would be switched on and off, drawing the flow through the inhaler for a pre-determined number of seconds.

1.7. Effect of inspiratory flow rate on DPI performance

1.7.1. Inspiratory flow rates in different patient groups

While *in-vitro* testing of DPIs was performed largely at a flow rate of 60 litres.minute^{-1}, regardless of the air flow resistivity of the device being tested, clinicians began to conduct studies on what flows patients could achieve in practice through DPI devices (Engel, 1990; Spiro, 1992). These studies showed that the flow rates that patients achieved varied from one device type to another, and that wide ranges of flow rates were recorded for a single device in practice. For example, Dickens *et al* (1994) demonstrated that a healthy volunteer inhaling maximally through three commercially available DPIs achieved peak flow rates of approximately 40, 80 and 120 litres.minute^{-1}, a three-fold range. Timsina *et al* (1993) demonstrated that a group of healthy volunteers typically achieved a two to threefold range of flowrates through a given DPI, and a fourfold range across four commercially available DPIs.

1.7.2. Effect of flow rate and other parameters on DPI performance

Awareness that wide variations in flow rates through DPI devices were common in practice led naturally to the examination of inhaler performance across a range of flow rates. Studies showed that some DPIs were more susceptible to the effects of flow rate than others, but most were affected to some degree by inhalation flow rate (Hindle and Byron, 1995; DeBoer *et al*, 1996). Current DPI products depend on the patient's inhalation through the device to aerosolise and emit the dose. If the airflow is zero, no dose will be emitted and therefore every DPI has a minimum flow rate at which powder

is emitted. Not surprisingly, for many DPIs the emitted dose will climb from zero to an acceptable value over a range of increasing flow rates and may then plateau at this level of performance or continue to climb throughout the range of flow rates achieved by patients. Ideal DPI behaviour would be to achieve a performance plateau at a flow rate below that achieved by any patient group.

1.7.3. Device resistance to airflow; pressure drop and flow rate relationships

As clinical studies have shown, patients are able to achieve higher flow rates through some DPIs than others. This is because DPIs vary in their resistance to air flow. When a patient starts to inhale, a low pressure, or partial vacuum, is generated on the 'lung' side of the inhaler. Atmospheric pressure then forces air through the inhaler to reduce the pressure difference, or pressure drop. The higher the resistance provided by the inhaler, the less rapidly the air is able to pass through and equalise the pressure on either side of the restriction. Hence a high resistance inhaler results in a greater pressure drop across the inhaler and a lower flow rate, while a low resistance inhaler will result in a high flow rate and a smaller pressure drop. In practice, the relationship between resistance, pressure drop and flow rate is described by equation 1.1:

Equation 1.1

$$Q = \sqrt{\Delta P} / R$$

Where Q = flow rate (litres.minute^{-1})

ΔP = pressure drop (kPa)

R = specific resistance, or resistivity (kPa$^{0.5}$.litres^{-1}.minute)

(Ower and Pankhurst, 1977)

1.8. Attempts to develop realistic tests for DPIs

From the early 1970s, when the first DPIs appeared through to the early 1990s all DPIs were typically tested at a single flow rate, 60 litres.minute^{-1}. A combination of clinical studies on patient flow rates and *in-vitro* studies on varying performance of DPIs at different flow rates highlighted the need for better comparative test conditions which would allow a fair comparison of one product against another and mimic patient use to a greater degree.

The first paper to clearly describe a relationship between flow rate and DPI resistance, and the implications for *in-vitro* testing was Clark and Hollingworth (1993). A series of experiments were described in which the resistivities of a number of commercially available DPIs were first determined, and then model inhalers were made with resistivities covering, and extending, that range. These model inhalers were used for flow rate measurements by healthy volunteers, who were asked to inhale at a 'comfortable' inspiratory effort and at maximum effort. The data showed that above a certain level of device resistivity, a maximum pressure drop was achieved, equal to approximately 80cm H_2O (7.85 kPa). The resistivity of the human airways was also derived from the volunteer data. On this basis, the suggested approach to selecting a flow rate for *in-vitro* testing was to use a flow rate up to that corresponding to 80cm H_2O pressure. The equation which calculated the flow rate included a term which allowed for the resistivity of the airways as well as the resistivity of the inhaler itself. An in-depth discussion of the study and its conclusions is included in section 4.7.1. Another study, reported in 1994 (Olsson and

Asking), also attempted to derive a relationship between device resistance and inspiratory flow rate. In this study, healthy volunteers were asked to inhale maximally through a series of constrictions with varying resistance to air flow. An empirical equation was fitted to the data. This equation included the pressure drop across the constriction at a flow rate of 60 litres.minute^{-1}, the peak flow rate achieved, and a characteristic parameter for each subject, which the authors termed the 'inspiratory force, although it is not a true force in the strict physical sense'. A limited data set on mild asthmatic subjects was found to be consistent with the empirical equation based on healthy volunteers. Three values of the inspiratory force were suggested as representative of weak, moderate and strong inhalations. The equation allowed flow rates for *in-vitro* testing to be calculated for any device of known resistance. This paper will be discussed further in section 4.7.2.

In 1994 the United States Pharmacopeia's Advisory Panel on Aerosols proposed a 'recipe for determining the airflow to be used' for testing a given DPI. (Byron, 1994). The recipe grouped DPIs into three broad categories of resistivity; those with $R \geq 0.12$ (cm $H_2O)^{0.5}$ litres^{-1} minute which should be tested at 30 litres.minute^{-1}, those with $R \leq 0.07$ (cm $H_2O)^{0.5}$ litres^{-1} minute which should be tested at 100 litres.minute^{-1}, and those with values of R falling between those two limits which should be tested at 60 litres.minute^{-1}. These limits were not apparently based on the published study by Clark and Hollingworth, even though the method of determining device resistivity was attributed to them. In 1996, after considerable debate in both USA and European pharmacopeial bodies, an alternative and harmonised approach based on pressure drop was suggested. This approach (Ganderton and Byron, 1996) proposed that a pressure drop of 4 kPa was representative of what patients could maintain across an inhaler, and therefore whatever flow rate corresponded

to 4 kPa for a given inhaler should be used for testing the device. This proposal, which supported a misconception that pressure drop equated to inspiratory effort across device types, was adopted and published in both pharmacopoeias (British Pharmacopoeia, 2002).

It is a misconception that because pressure drop is proportional to inspiratory effort for a given device, it is proportional to inspiratory effort across devices of differing resistivities. It is useful here to define the measure of inspiratory effort as the pressure drop, or pressure difference, that a subject can achieve between the mouth and the external atmosphere when inhaling against an infinite, or near infinite, resistance. When inhaling maximally, this is termed the Maximum Inspiratory Pressure (MIP), in kPa. A subject inhaling maximally, and consistently, through devices of differing resistivity will achieve a different flow rate and pressure drop through each device, although applying the same inspiratory effort each time. For a given device, the higher the inspiratory effort applied, the higher the pressure drop will be, so in this case pressure drop is proportional to inspiratory effort. However, it has sometimes been mistakenly suggested that when the same pressure drop is achieved with two or more DPIs of different resistivity, that the same inspiratory effort has been applied. This mistake first appeared in the literature in 1992 (Sumby *et al*).The authors concluded that to achieve a flow rate of 60 litres.minute^{-1} the inspiratory effort required through one device, the Turbuhaler, was more than twice that required for the Diskhaler because the pressure drop across the two devices at 60 litres.minute^{-1} was 3.92 kPa and 1.80 kPa respectively. Soon after two hospital clinicians (Richards and Saunders, 1993) suggested that DPIs should be tested at fixed values of pressure drop. They tested a number of DPIs for resistance across a range of

flow rates. The results highlighted the wide range observed. However, in a similar conclusion to Sumby *et al*, the paper suggested that since a three-fold increase in pressure drop was necessary in a (high resistance) Turbuhaler to achieve an equivalent flow rate to a (medium resistance) Diskhaler, that three times the effort would be needed to achieve it. In this way the misconception was propagated.

1.9. A statement of the problem

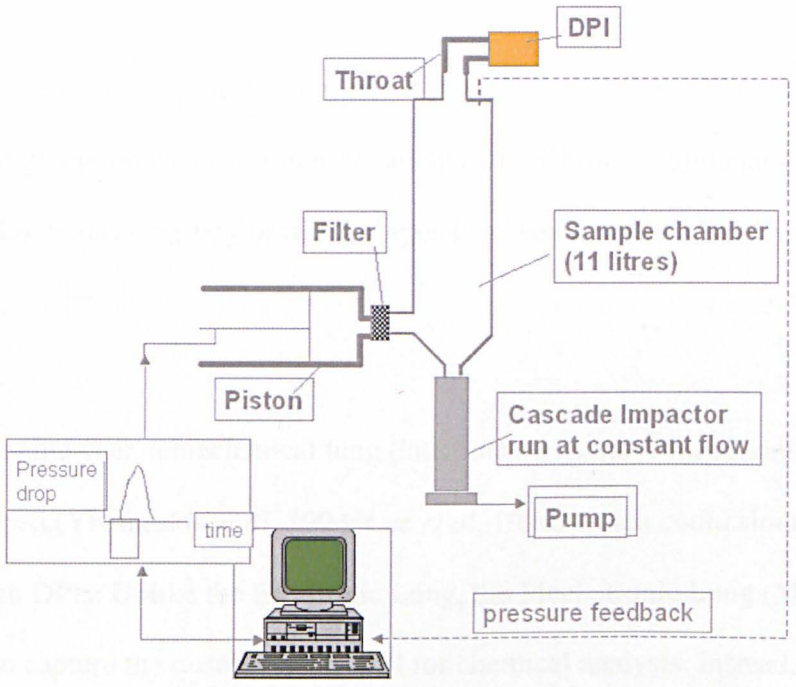
It is known that the range of flow rates which patients can achieve through a DPI is related to the resistance to airflow offered by that device. It has also been established that the performance of a DPI can vary with the flow rate (and possibly with other characteristics) of inhalation. A fair comparison of performance for DPIs requires that they should be tested with an equivalent level of inspiratory effort. Current pharmocopeial methods do not provide the basis for such tests, being based on a single pressure drop, which does not equate to consistent inspiratory effort when applied to different inhalers. Similarly, testing at a single flow rate, which has been common practice in the pharmaceutical industry, does not apply a consistent inspiratory effort when applied to inhalers with differing resistivities. Two studies, based on inhalation profiles measured in healthy volunteers or asthmatic patients have attempted to derive a relationship between inspiratory effort, device resistance and flow rate, which may be applied to *in-vitro* testing. It is difficult, however, for human subjects to be consistent in their inspiratory effort, particularly when switching between devices of varying resistivity. Consequently, the levels of variability included in human-based studies may obscure an exact relationship between these parameters. A mechanical device, which

could inhale with consistent inspiratory effort, and which would 'react' to changes in device resistance was required, in order that the relationship could be studied without the variability associated with human subjects. Such a device would also enable practical *in-vitro* testing of dry powder inhalers at consistent levels of inspiratory effort.

1.10. Review of mechanical lungs in *in-vitro* testing

The first mechanical lung developed to generate patient inspiratory profiles through DPI products was the Electronic Lung described by Brindley *et al* (1994). The Electronic Lung consists of a computer-controlled piston, a sampling chamber, a 'throat', and a Cascade Impactor (Figure 4).

Figure 1.4 The Electronic Lung



The computer-controlled piston draws an 'inhalation' through the DPI, which is fitted in the throat above the sampling chamber. The inhalation profile may be recorded from a patient's inhalation or manually programmed into the computer. If a patient inhalation is to be used it is first recorded as a pressure drop/time profile when the patient inhales through a modified inhaler of the chosen type fitted with a pressure probe in the mouthpiece. The Electronic Lung can reproduce this pressure drop/ time profile, but the correct inhaler type must be used or the pressure drop will not generate the correct flow rate. The dose is drawn from the DPI, through the throat and into the sampling chamber by the movement of the computer-controlled piston. When the inhalation is complete, the switching valve connecting the piston to the sampling chamber closes and the valve connecting the sampling chamber to the Cascade Impactor opens. The aerosolised particle cloud is then drawn through the Cascade Impactor at the constant flow rate required for particle sizing.

The Electronic Lung has been used for a number of studies where the ability of different patient groups, such as children or patients with Chronic Pulmonary Obstructive Disease (COPD), to use a variety of inhaler types has been assessed (Small *et al*, 1997; Burnell, 1996).

In the same year, a mechanical lung (later known as the 'Mechatronic Lung') was described (Yianneskis *et al*, 1994; Lee *et al*, 1996) which could simulate inhalations through DPIs. Unlike the Electronic Lung, the Mechatronic Lung (ML) apparatus was not used to capture the dose from the DPI for chemical analysis. Instead, the emitted cloud of

particles was examined by laser-sheet flow visualisation and laser-Doppler anemometry as it entered a clear chamber simulating the mouth cavity.

The air flow through the ML is generated by a fan and adjusted to the desired peak flow rate. The inhalation profile is achieved by means of a cam-driven double-seated valve mechanism. The cam is traversed by a variable speed motor and moves the valve between two positions corresponding to the start and end of the inhalation. The shape of the profile is determined by the cam profile as it moves the valve and the duration is determined by the traversing speed. The inhalation profiles used in device testing were based on the averaged profiles of healthy volunteers using the appropriate DPIs. The ML was used to study the velocity and the degree of turbulence of particles emitted from several DPIs at 25, 50, 75 and 100% of the average maximum inhalation pressures achieved by the healthy volunteers, in order to simulate varying inspiratory efforts.

An electronic lung based on feedback control of a needle valve was developed by Clark and Bailey (1996). A programmable controller monitored the flow rate through a mass flow meter and adjusted the needle valve automatically to achieve the desired inhalation profile. Using a similar approach to the ML, a laser photometer was used to determine the size distribution of the aerosolised cloud emitted from the DPI being tested. The inhalation profiles used in the study were not real or simulated human profiles, but employed varying flow acceleration rates or stepped flows to examine DPI performance characteristics.

The mechanical lungs used in *in-vitro* testing to date have been designed to reproduce or to artificially create human or varied inhalation profiles through DPIs in order to study

device performance. All of these lungs generate a pre-determined flow rate or pressure drop through the test device, and attempts to investigate different levels of inspiratory effort have been based on selection of appropriate pressure or flow values. None of these lungs have been designed to compare DPIs at a given level of inspiratory effort and allow the flow rate or pressure drop to vary naturally with the resistivity of the device.

1.11. Ideology of thesis

The objective of the work described in this thesis was to develop and test a mechanical lung which could inhale with consistent inspiratory effort, and which would 'react' to changes in device resistance like a human; achieving higher flow rates at lower resistivities. The lung would be used to explore the relationship between DPI resistivity, inspiratory effort and the characteristics of inhalation profiles, principally pressure drop, but also flow acceleration rate. Such a test apparatus would also allow examination of new approaches to the practical testing of DPIs which had not been previously possible.

2. DESIGN OF THE HYDRAULIC LUNG

2.1. Early concepts

2.1.1. The Vertical Syringe

The first design for a mechanical lung that would inhale at a fixed level of inspiratory effort was essentially a vertical syringe, as shown in Figure 2.1.

A weight attached to the piston and able to fall would simulate the inspiratory effort generated by the chest muscles. Varying the mass would allow the inspiratory effort to be varied, simulating the inhalations of a healthy adult or an asthmatic child, for example. A DPI placed in the 'mouth' of the apparatus would offer resistance to air entering the 'lung cavity' or body of the syringe thereby restricting the rate at which the piston could fall, in the same way that a DPI restricts the rate of expansion of the lungs.

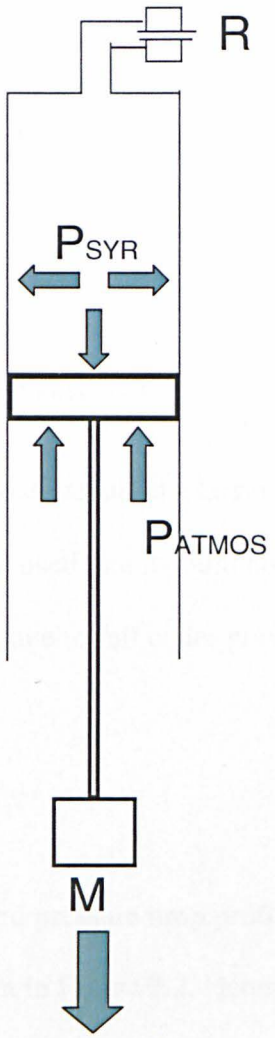
The key forces acting on the syringe (without considering friction at this stage) are also shown in Figure 2.1. Downward forces acting on the piston are due to gravity, g, acting on the mass, M, and the pressure exerted by air within the syringe, P_{syr}. The upward (opposing) force acting on the piston would be due to atmospheric pressure, P_{atmos}. Since the forces due to gravity and to atmospheric pressure would remain constant within an experiment, the balance between the two sets of forces, and hence the movement of the piston, would vary with changes in P_{syr} as the internal volume of the syringe changed and air was able to enter the syringe through the DPI.

The pressure drop and flow profiles which might be generated by such an apparatus are best illustrated by first considering the extreme cases of infinite and zero resistance DPIs.

2.1.1.1. Infinite Resistance

In the case of a DPI with infinite resistance, no air would be able to enter the syringe. When released, the weight and piston would fall, increasing the volume within the syringe. The pressure within the syringe would fall, reducing the downward forces.

Figure 2.1 Forces acting within the Vertical Syringe Model



At some point, the downward forces would be exceeded by the upward force due to atmospheric pressure and the movement of the piston would be slowed. In an idealised system, with no friction or other sources of energy loss, the piston would be likely to oscillate around an equilibrium point (the null position) where the upward and downward forces were balanced. In a realistic system, with energy losses due to friction and adiabatic effects the piston would settle at this position, either with or without some oscillation.

Since force = mass x acceleration, and force = pressure x area (in this case the area of the piston surface), when the weight is released:

$$M.g + P_{syr(initial)}.area > P_{atmos}.area$$

When the forces are balanced at the equilibrium point:

Equation 2.1

$$M.g + P_{syr(end)}.area = P_{atmos}.area$$

Clearly, increasing the mass, M, would result in a larger pressure drop ($\Delta P = P_{atmos}.- P_{syr(end)}$) until such a large mass was used that it could not be equalised by atmospheric pressure and the piston would continue to fall under gravity until it reached the end of its permissible travel i.e.

$$M.g/area > P_{atmos}$$

If the forces balanced the anticipated pressure drop profiles generated in idealised and realistic systems would be as shown in Figure 2.2. Hereafter, only realistic profiles will be considered. Flow would remain at zero, as illustrated in Figure 2.3.

Figure 2.2 Anticipated pressure drop profiles of Vertical Syringe with infinite resistance device

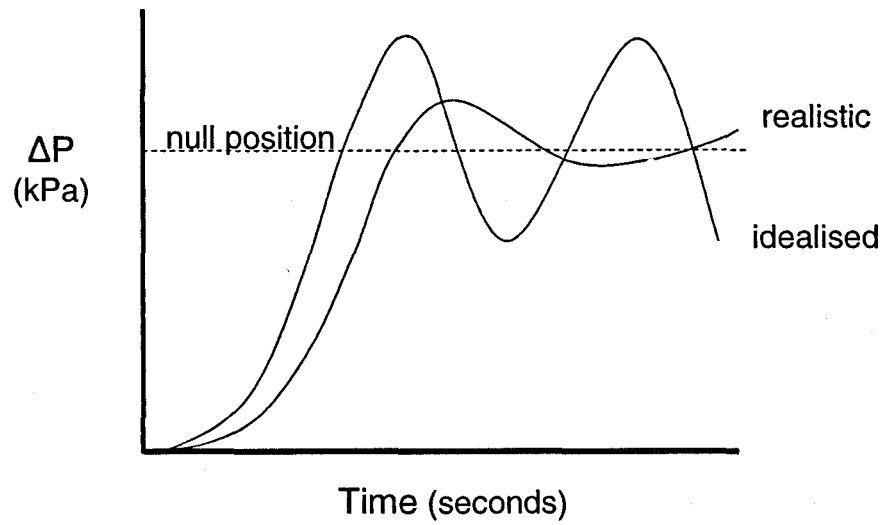
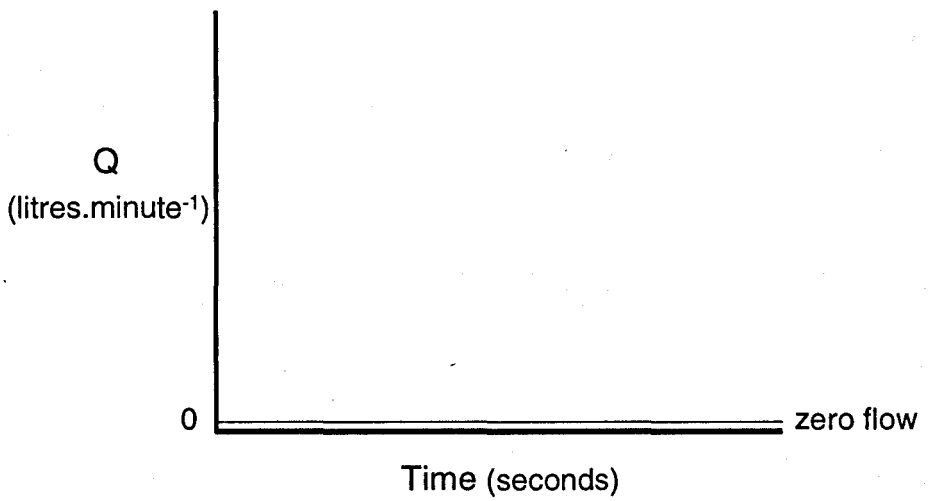


Figure 2.3 Anticipated flow profile of Vertical Syringe with infinite resistance device



2.1.1.2. Zero Resistance

In the alternative extreme case where no resistance to airflow occurred, the piston would fall, as before, when released but air would be able to enter instantaneously such that no

difference in pressure between the interior of the syringe and the atmosphere would result. The piston would therefore fall under gravity until it reached the end of its permissible travel (the full capacity of the 'lungs'). In this case:

Equation 2.2

$$P_{syr(end)} = P_{atmos}$$

And $\Delta P = 0$

The flow profile would be as shown in Figure 2.4, and the pressure drop would be zero as shown in Figure 2.5

Figure 2.4 Anticipated flow profile of Vertical Syringe with zero resistance device

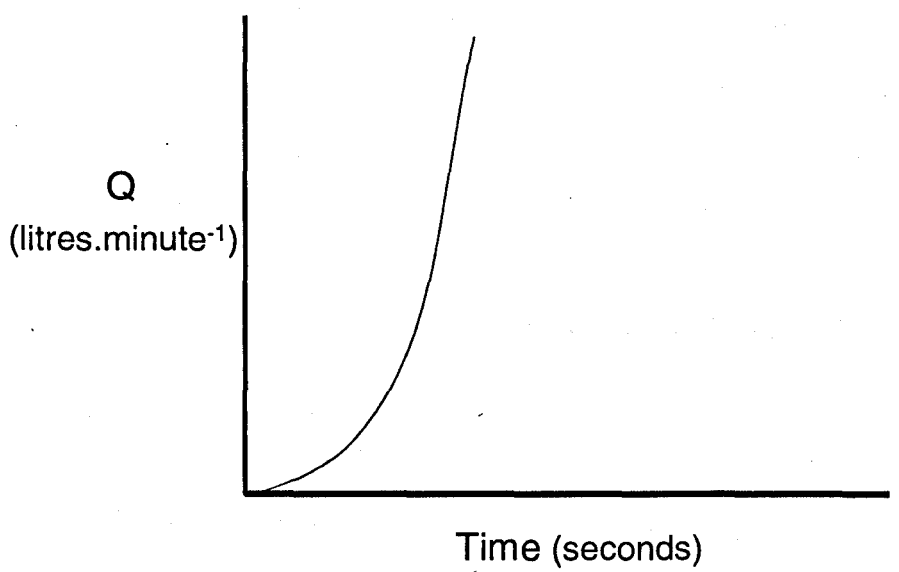
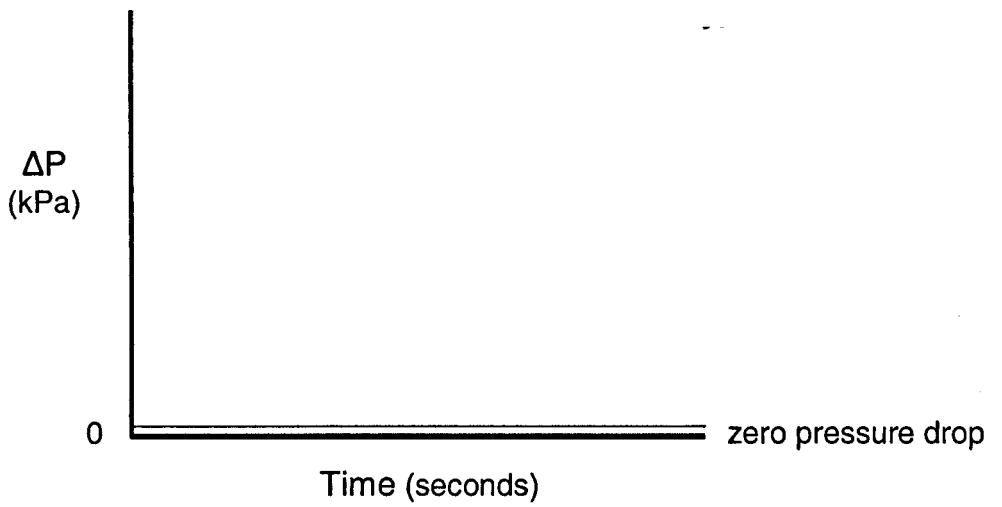


Figure 2.5 Anticipated pressure drop profile of Vertical Syringe with zero resistance device



2.1.1.3. Intermediate Resistance

If the resistance of the device were intermediate, i.e. greater than zero but less than infinite, the pressure drop and flow profiles would be expected to fall between the two extremes, having the shapes illustrated in Figures 2.6 and 2.7. It can be seen that the rate of fall of the piston would reach a constant rate as air entering the syringe achieved a steady state. This resultant profile is unlike a human profile in this respect; where flow rate typically reaches a maximum and then diminishes to zero as the total lung capacity is achieved.

Figure 2.6 **Anticipated pressure drop profile for Vertical Syringe with intermediate resistance device**

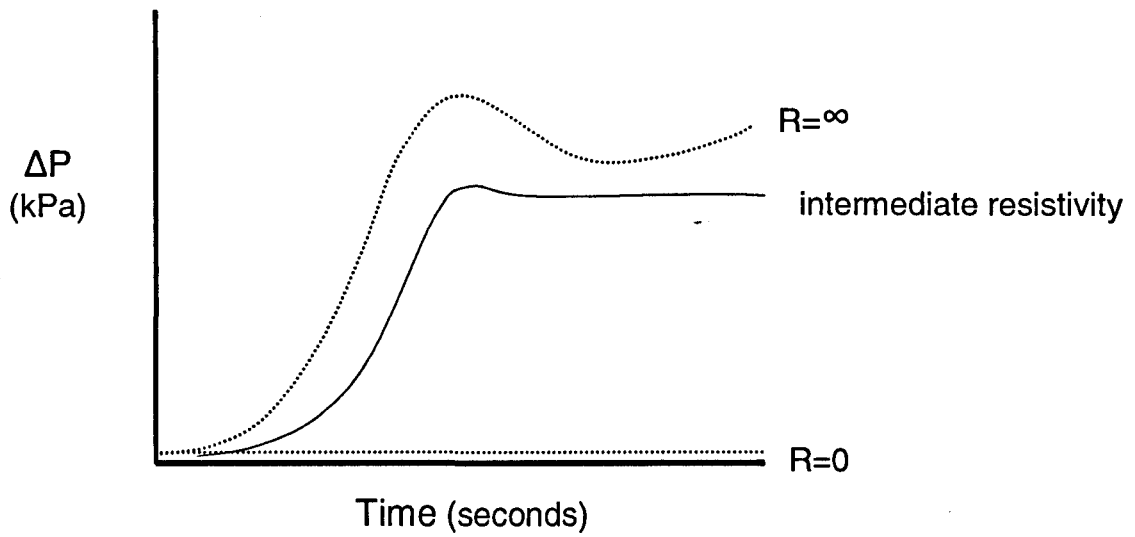
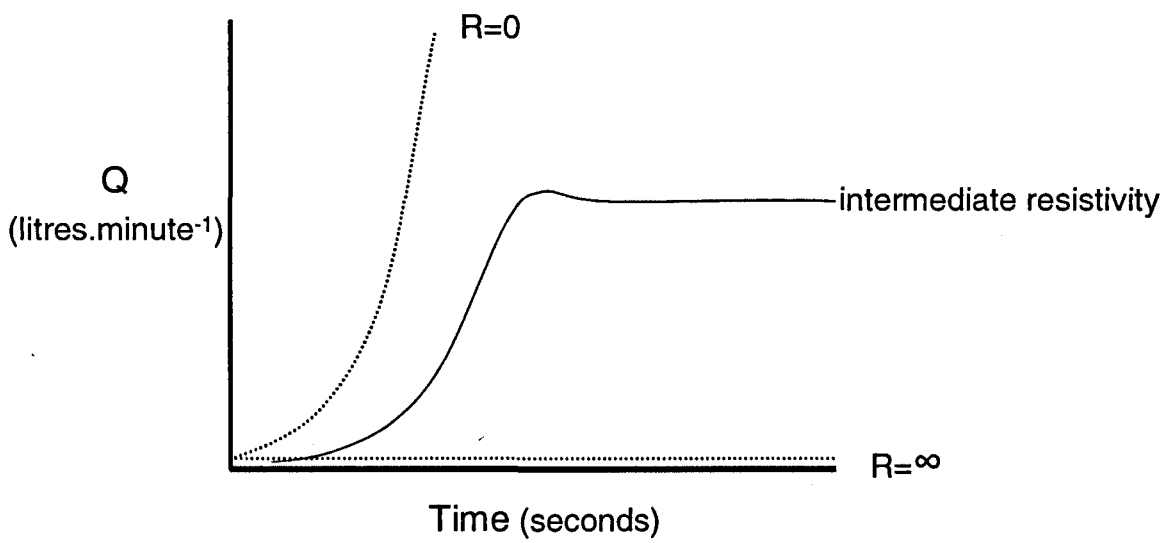


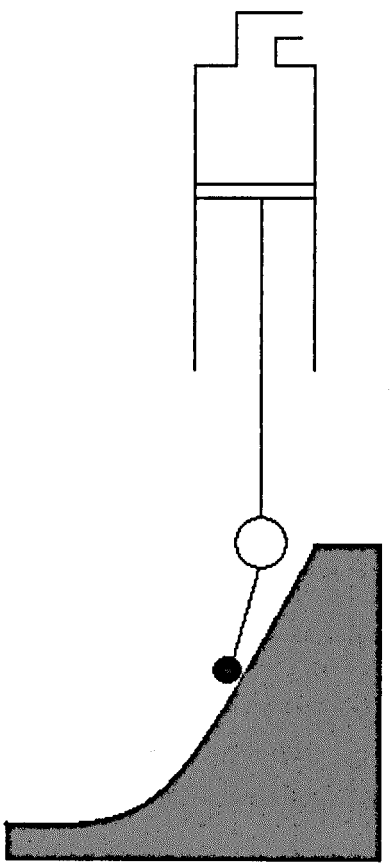
Figure 2.7 **Anticipated flow profile for Vertical Syringe with intermediate resistance device**



In order for the syringe apparatus to have a declining profile after the maximum pressure was achieved, the force acting downwards on the piston would have to decline until a balance of forces was achieved. Numerous means of achieving this could be devised for a

mechanical apparatus. One such design is shown in Figure 2.8. In this version the mass falling under the acceleration due to gravity is attached to the piston by a string. Rather than falling vertically, the mass descends a slope which ends in a horizontal plane.

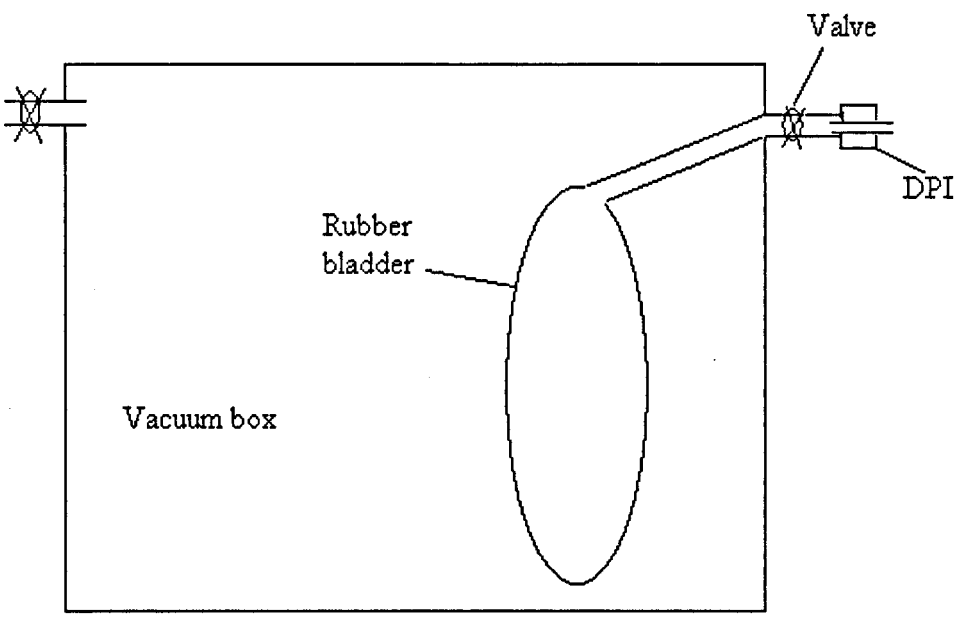
Figure 2.8 Modified Inverted Syringe Model



2.1.2. The Bladder in a Vacuum

This concept, suggested by Dr P. Burnell (1999) is shown in Figure 2.9.

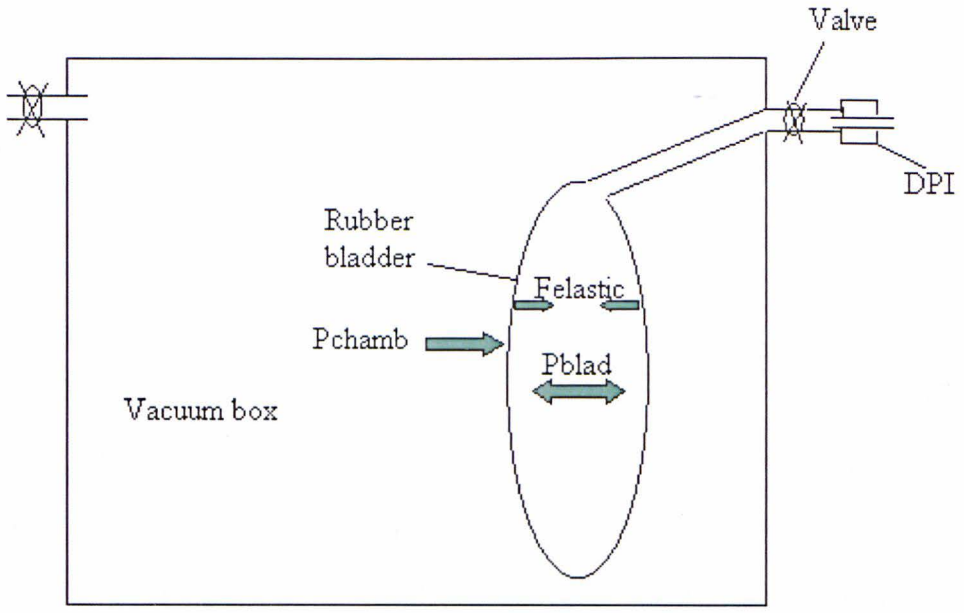
Figure 2.9 The Bladder in a Vacuum



The apparatus consists of a rubber bladder inside an enclosed compartment. The bladder would have approximately the same volume as a pair of average human lungs when fully inflated. Before inhalation, the bladder would be deflated (its 'rest' position), the 'mouth' of the apparatus would be sealed by a valve, and the air from the chamber would be evacuated by a vacuum pump. The vacuum pump would be switched off and the mouth valve opened to initiate the inhalation. Forces acting on the system are shown in Figure 2.10. At the beginning of the experiment, before the mouth valve was opened, the pressure within the bladder $P_{blad(initial)}$ would be approximately equal to the pressure inside

the chamber $P_{chamb(initial)}$, assuming that the resistance offered by the bladder, $F_{elastic}$, at this stage was small.

Figure 2.10 Forces acting in the Bladder in a Vacuum



Both $P_{blad(initial)}$ and $P_{chamb(initial)}$ would be lower than P_{atmos}.

Equation 2.3

$$P_{blad(initial)} \approx P_{chamb(initial)} < P_{atmos}$$

When the valve was opened, atmospheric pressure would drive air into the bladder at a flow rate determined by the resistivity of the DPI and the pressure drop across it.
As air entered the bladder the pressure within the bladder would become greater than the pressure in the chamber, causing the bladder to expand. Forces resisting the expansion of the bladder are:

$$P_{chamb} + F_{elastic}/area$$

The pressure within the chamber, the elastic resistance of the bladder and the area of the bladder will all change as the bladder expands. The pressure within the chamber can only increase from its initial value. The area of the bladder can only increase, and this may counter any increase in the elastic resistance of the bladder. The extent to which this is the case will depend on the elastic properties of the bladder. It is therefore difficult to predict the shape of pressure drop and flow profiles which would be generated by the apparatus. At some point it is anticipated that the pressure in the chamber and the elastic resistance of the bladder would increase sufficiently to prevent further expansion of the bladder. The pressure within the bladder would equal atmospheric pressure and both pressure drop and flow would be zero. However, the apparatus would provide a high initial instantaneous value of both pressure drop and consequently flow rate and this would not therefore resemble a human inhalation profile.

2.2. Advantages of a hydraulic system

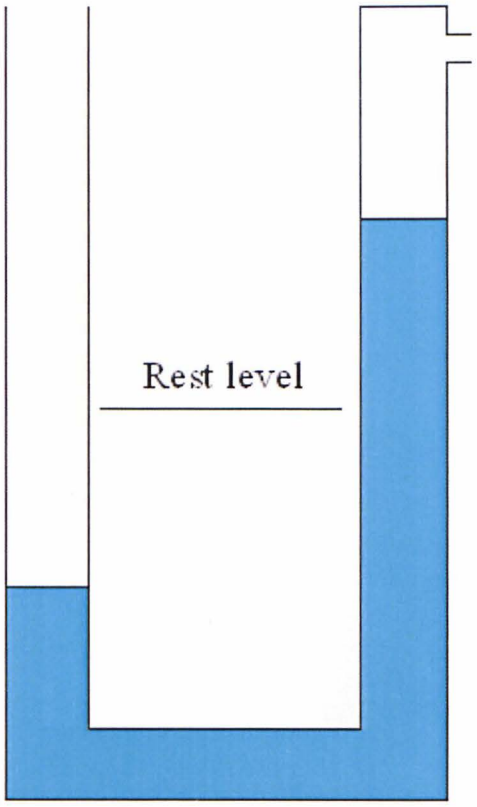
The two early concepts have different advantages and disadvantages as practical tools for the study of DPI performance and the relationships between device resistance, inspiratory effort, flow rate and other inhalation characteristics. Some of these are summarised in Table 2.1.

Table 2.1 Advantages and disadvantages of early concepts

System	Advantages	Disadvantages
Vertical Syringe	Simple to adjust 'inspiratory effort' by varying mass Human-like inspiratory profile in early (acceleration) phase	Small temperature fluctuations or piston wear likely to affect friction, causing poor reproducibility Inspiratory profile reaches steady-state unless additional mechanism added to decrease effort Additional mechanism may also be subject to friction and variability
Bladder in a Vacuum	Simple to adjust 'inspiratory effort' by varying initial chamber pressure	Unrealistic inspiratory profile; significant flow at zero timepoint Rubber bladder elasticity might vary over time leading to poor reproducibility

The concept of the Hydraulic Lung, suggested by R.Adkins (1999) is to use a falling column of water as the piston in a vertical syringe type apparatus, in order to achieve highly reproducible friction. A declining inspiratory effort is achieved by allowing the water to fall in a 'U' tube such that the 'head' of water in one arm decreases until the water finds its own level. This is illustrated in Figure 2.11. The Hydraulic Lung therefore has the advantages of the Vertical Syringe in terms of simple adjustment of inspiratory effort and human-like profile without the disadvantages created by potentially variable friction.

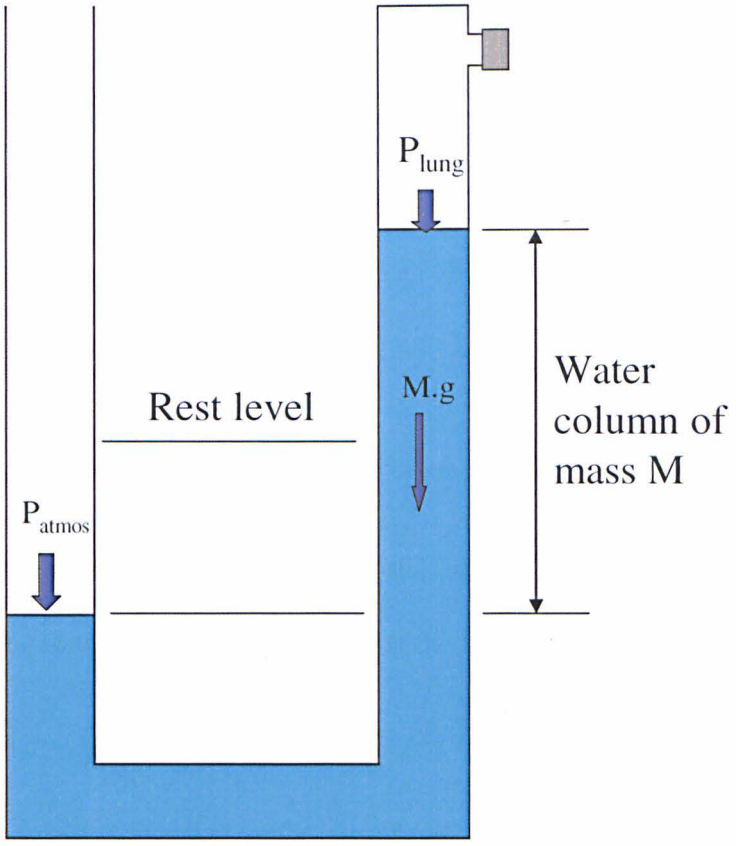
Figure 2.11 'U' Tube model



2.3. The Hydraulic Lung and refinements mimicking the human respiratory system

A diagrammatic illustration of the Hydraulic Lung concept is shown in Figure 2.12 with the forces acting on the water column (which is treated as frictionless, for simplicity).

Figure 2.12 Forces acting in the Hydraulic Lung model



At the point of release of the water column the downward forces acting on the water column are due to the mass, M, of the water column in the right arm which is above the water column in the left arm, falling under the acceleration, g, due to gravity and the pressure exerted by air within the lung, P_{lung}. The upward force acting on the water column in the right arm is due to the atmospheric pressure acting downwards on the surface of the water column in the left arm. The pressure drop and flow profiles which might be generated by a Hydraulic Lung are best illustrated, as for the vertical syringe, by first considering the extreme cases of infinite and zero resistance DPIs.

2.3.1. Infinite Resistance

For a DPI of infinite resistance, as the right water column falls under gravity the pressure in the lung falls, and the height of the water in the right arm above the left arm decreases the until the upward and downward forces are balanced, i.e.

Equation 2.4

$$M_{(end)}.g/area + P_{lung(end)}. = P_{atmos}.$$

At this stage the pressure difference between the interior of the lung and the external atmosphere is the maximum pressure drop that the inspiratory effort applied can generate.

Equation 2.5

$$\Delta P_{max} = P_{atmos}. - P_{lung(end)}$$

Therefore:

Equation 2.6

$$\Delta P_{max} = M_{(end)}.g/area$$

Equation 2.7

$$\Delta P_{max} = H_{(end)}.\pi r^2.\rho.g/\pi r^2 = H_{(end)}.\rho.g$$

This result is to be expected, as the apparatus at this point is acting much like a simple manometer. The pressure drop profile generated in this experiment would be expected to

look like that in Figure 2.13. The pressure drop would rapidly rise to the maximum value and then remain at a constant level. Flow would remain at zero, as shown in Figure 2.14.

Figure 2.13 Anticipated pressure drop profile in Hydraulic Lung with infinite resistance DPI

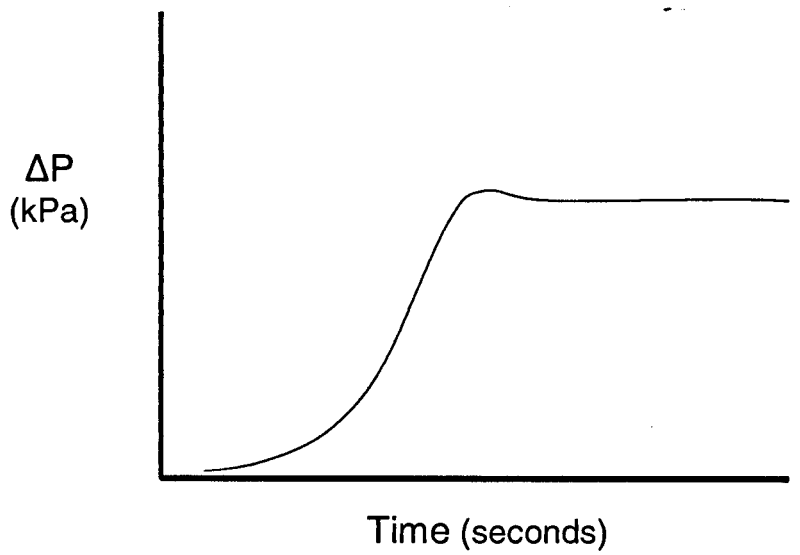
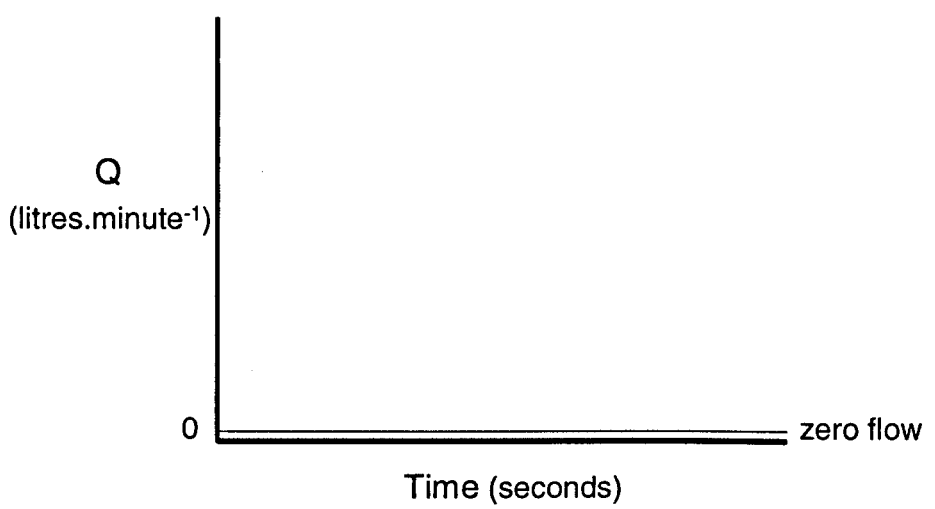


Figure 2.14 Anticipated flow profile in Hydraulic Lung with infinite resistance DPI



2.3.2. Zero Resistance

If the DPI (and the apparatus) offered zero resistance to air entering the lung the pressure drop would remain as zero throughout the experiment. The water column would fall with the acceleration due to gravity and air would enter the apparatus at the same rate, decreasing as it passed the equilibrium point. The water level, and therefore the air flow would probably oscillate briefly around the equilibrium point.. The anticipated pressure drop and flow profiles would look like Figures 2.15 and 2.16 respectively.

Figure 2.15 Anticipated pressure drop profile in Hydraulic Lung with zero resistance DPI

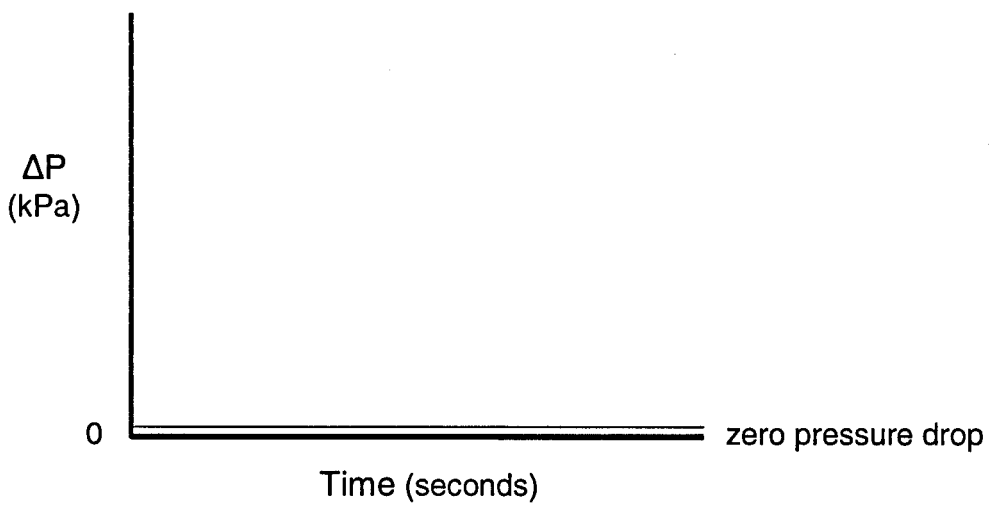
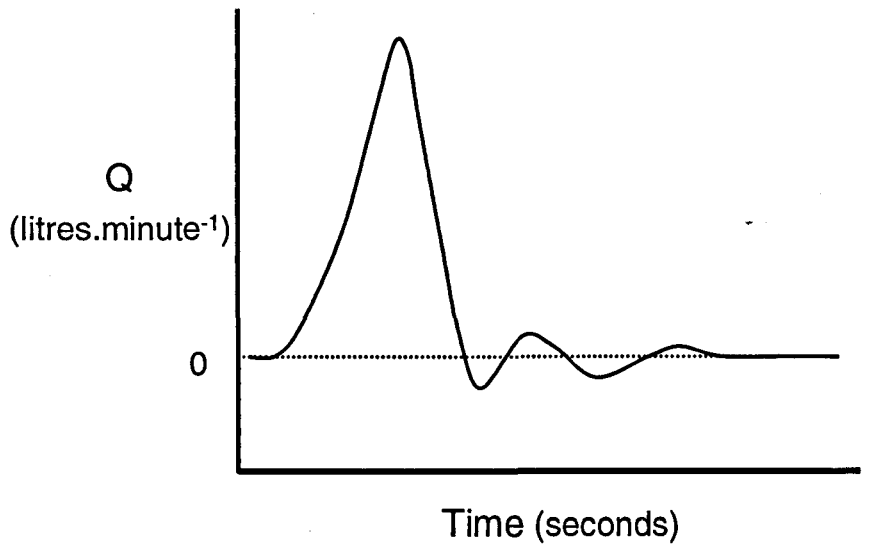


Figure 2.16 Anticipated flow profile in Hydraulic Lung with zero resistance DPI



2.3.3. Intermediate Resistance

In the case of a DPI with an intermediate resistivity, between zero and infinity, the pressure drop across the device would approach the maximum value to an extent determined by how closely the resistivity of the DPI approached infinity. An anticipated pressure drop profile is shown in Figure 2.17. Air entering the lung through the DPI would prevent the maximum value from being achieved and the declining downward force would result in a flow rate which declined to zero, as illustrated in Figure 2.18.

Figure 2.17 Anticipated pressure drop profile in Hydraulic Lung with intermediate resistance DPI

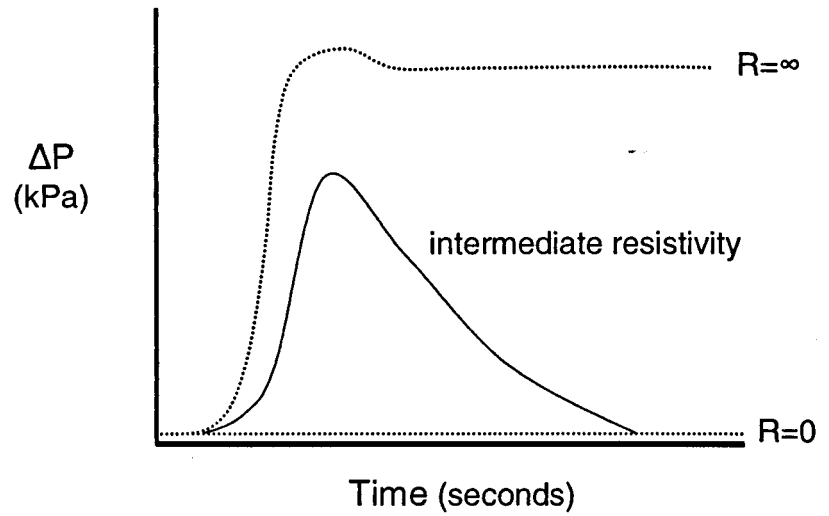
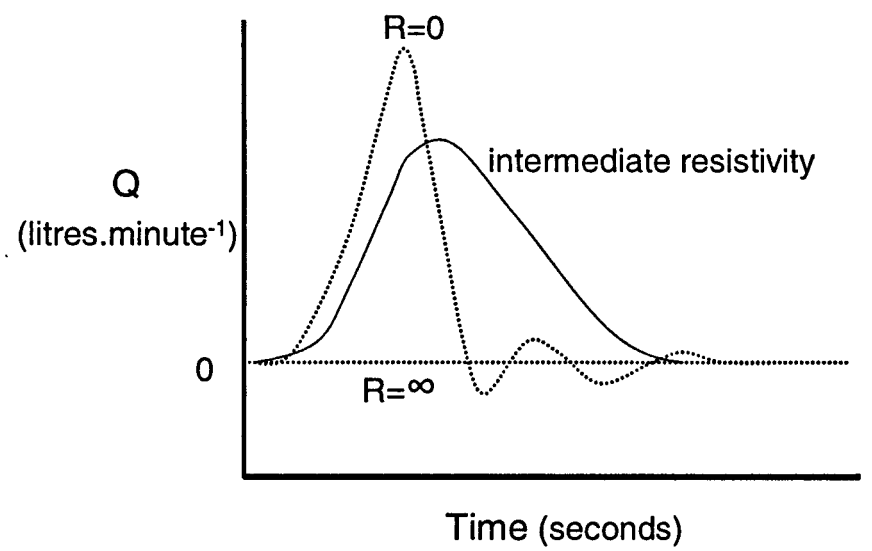
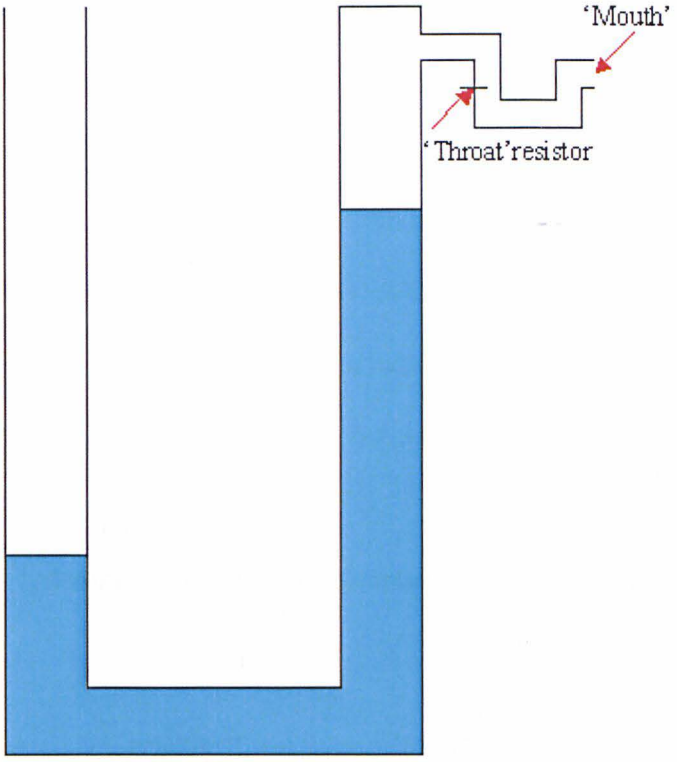


Figure 2.18 Anticipated flow profile in Hydraulic Lung with intermediate resistance DPI



The simple Hydraulic Lung model described above will generate a peak flow rate which continually decreases as DPI resistivity increases, for a given level of inspiratory effort. However, the human airways have a degree of resistance to airflow which depends upon anatomical variations and also on disease state (Green and Pride, 1981). Clark and Hollingworth (1993) suggested that the relative resistivity of the airways and the DPI would determine which resistivity dominated the relationship between pressure drop in the lungs and flow rate through the device. If device resistivity were significantly higher than the resistivity of the airways, the effect of the airways resistivity would be minimal. If the two resistivities were comparable, both would play a significant role in determining pressure drop across the device and the resultant air flow rate. The Hydraulic Lung has an orifice plate which can be used to vary 'airways' or 'throat' resistivity between the water column and the 'mouth' to simulate disease state or variations in anatomy and examine the effect on inhalation profile characteristics. This is shown in Figure 2.19.

Figure 2.19 Position of the throat resistor



2.4. Operation of the Hydraulic Lung

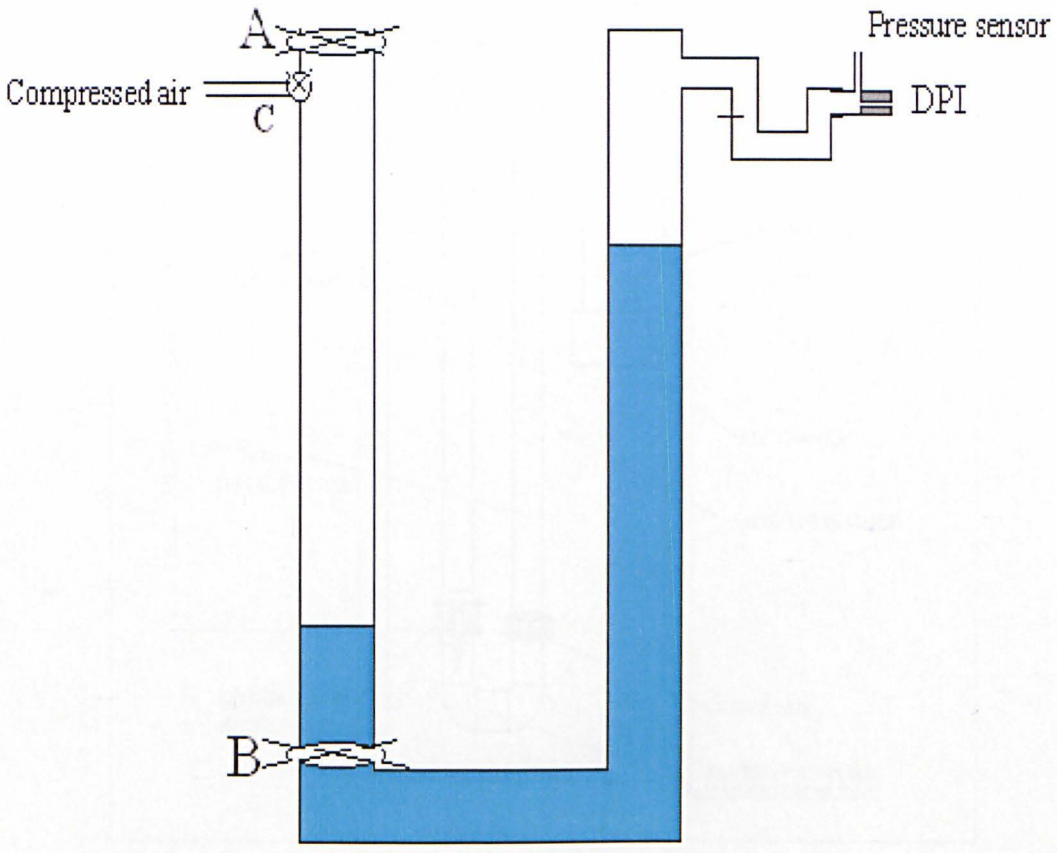
Before operating the Hydraulic Lung, the apparatus must be prepared as follows:

- The desired throat resistor must be fitted into the apparatus.
- The volume of water in the system must be adjusted to provide the required fall between the initial level and the rest level, i.e. the level of inspiratory effort must be set.
- The DPI to be tested must be fitted into the 'mouth' of the apparatus using a rubber adaptor to provide an airtight seal.
- The pressure sensor, if required, must be attached to the DPI.

The Hydraulic Lung is operated by the following sequence (valves are illustrated in Figure 2.20):

1. Close valve A and open valve B
2. Open valve C to allow compressed air into the apparatus
3. When the water level in the right tube reaches the initial level close valves C and B
4. Open valve A to release the pressure in the left tube
5. Open valve B, sharply, to perform the inhalation

Figure 2.20 Hydraulic Lung operating valves



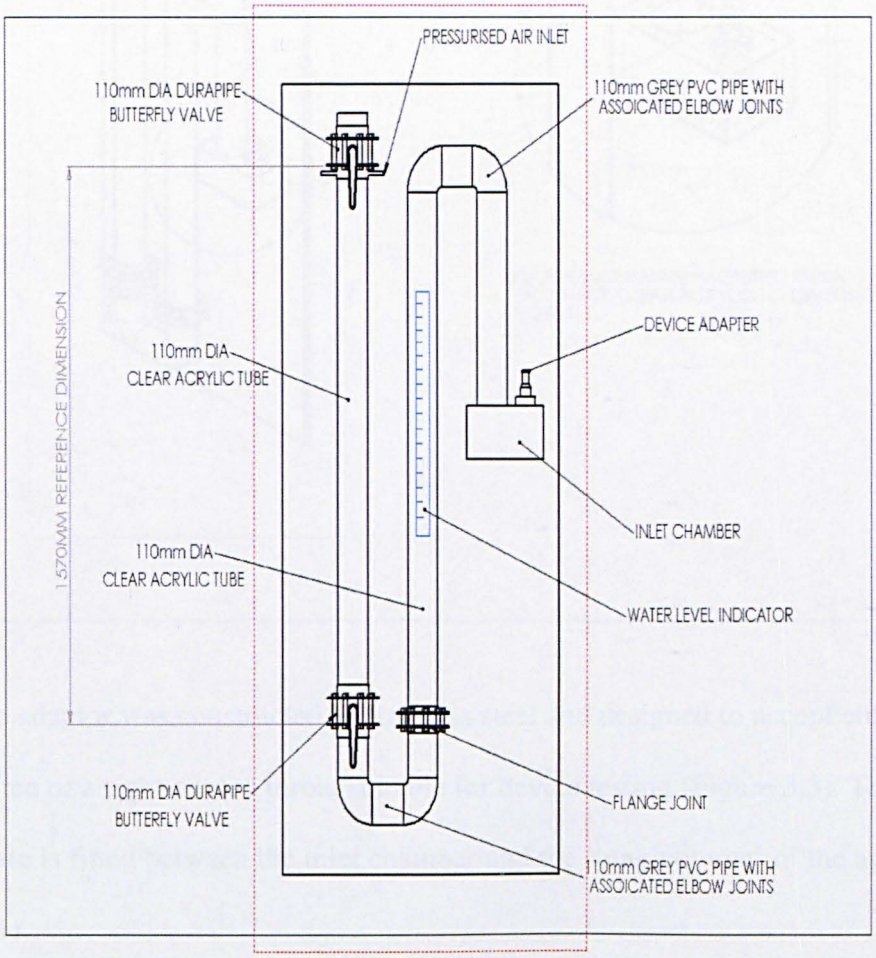
3. MATERIALS AND METHODS

3.1. Construction of the Hydraulic Lung

The Hydraulic Lung was constructed by the Applied Technology Unit at GlaxoSmithKline Research and Development with direction from R. Adkins of Cranfield University.

The materials used in the construction, and the key dimensions of the Hydraulic Lung are shown in Figures 3.1 and 3.2.

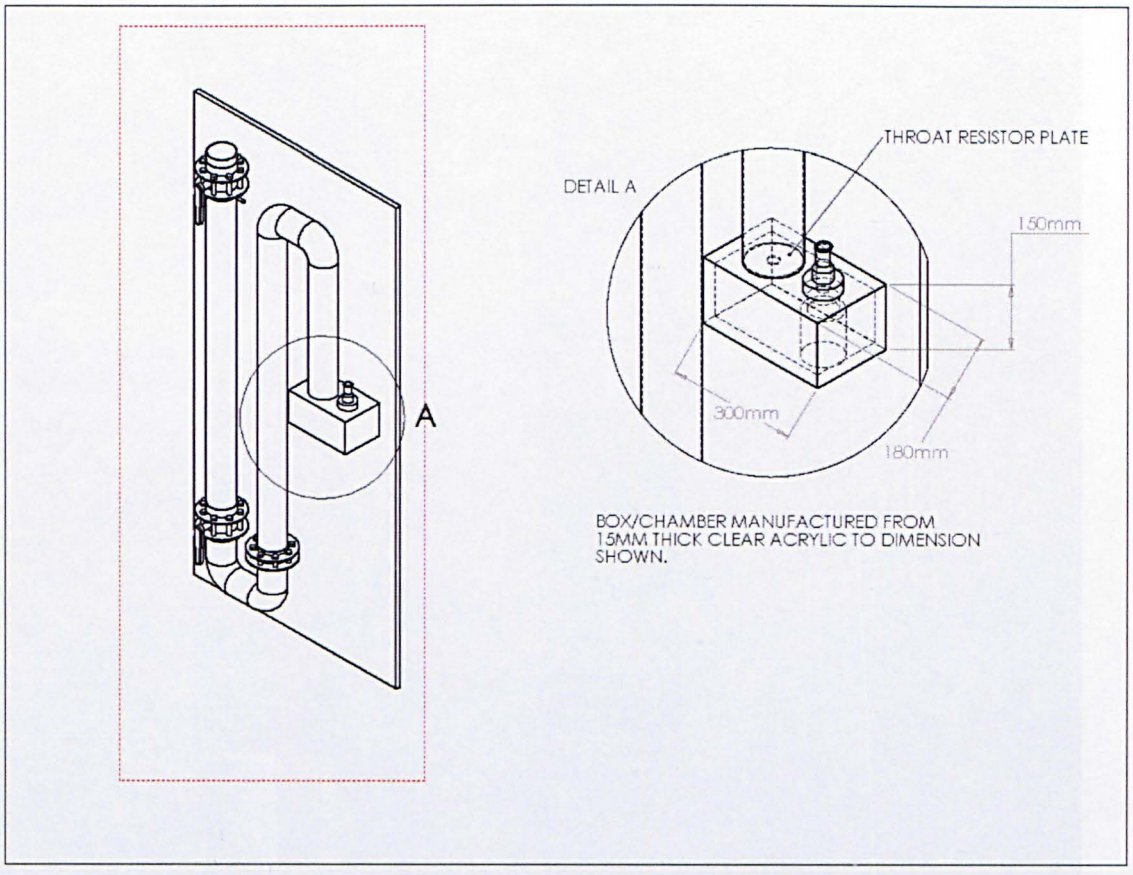
Figure 3.1 The Hydraulic Lung



Clear acrylic tubing was used for the right and left arms so that water levels would be visible. Elbow joints and connecting tubes were of the same diameter (110mm).

The inlet chamber (Figure 3.2) was also constructed of clear acrylic, large enough to allow either a low resistance electrostatic filter to be fitted below the mouthpiece for dose capture, or liquid capture if desired.

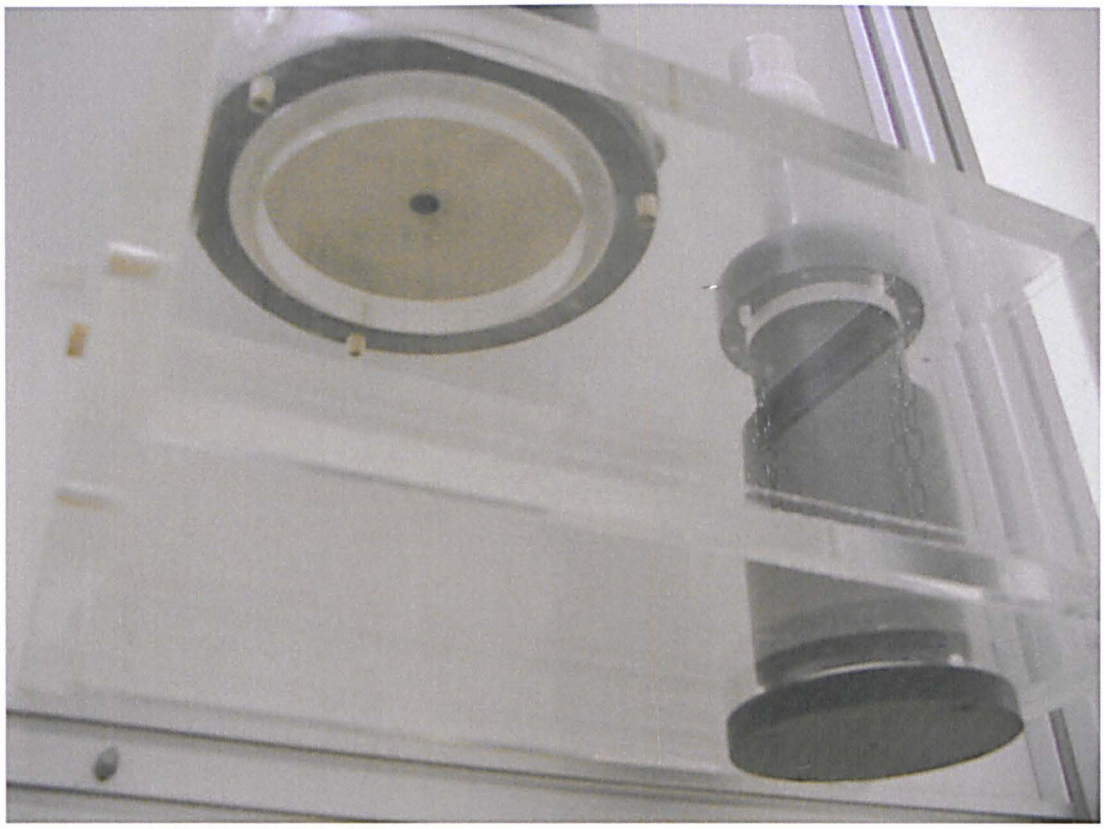
Figure 3.2 The inlet chamber



The device adaptor was constructed of stainless steel and designed to accept either the model device or a right-angled throat suitable for device testing (Figure 3.3). The throat resistor plate is fitted between the inlet chamber and the 'lung volume' of the apparatus (Figure 3.4).

Figure 3.3 The device adaptor and inlet chamber

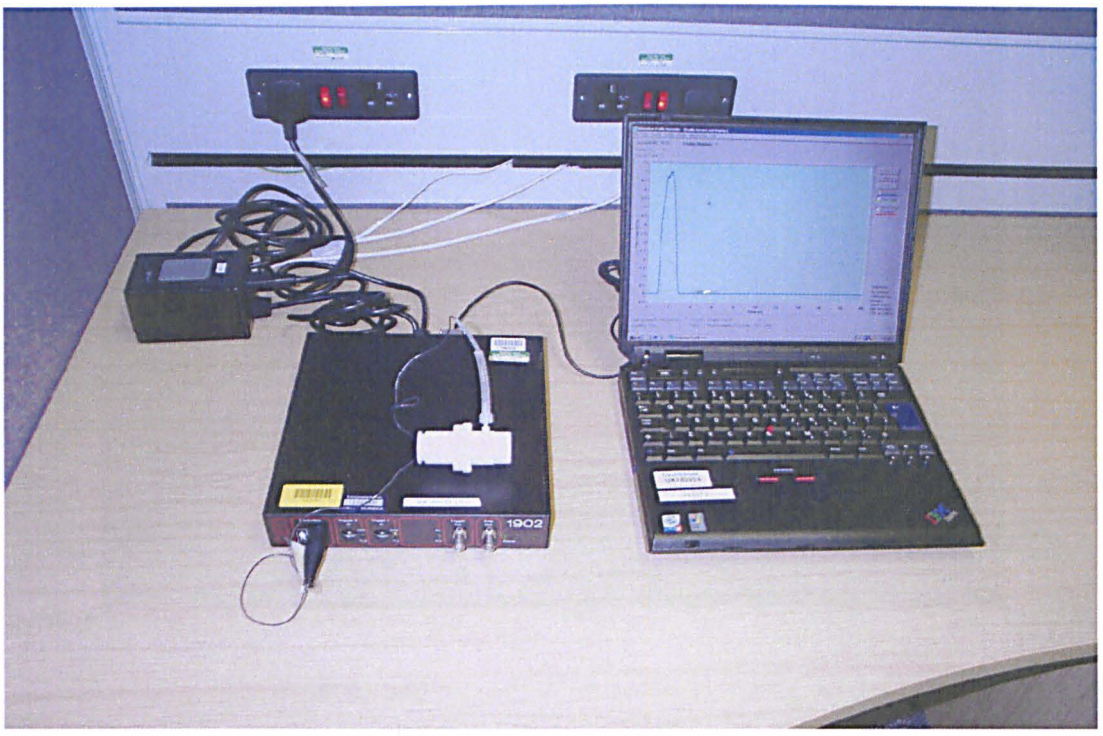
Figure 3.4 The inlet chamber and throat resistor (seen from below)



3.2. The inhalation profile recorder

The inhalation profile recorder (Figure 3.5) developed by GlaxoSmithKline Research and Development was used throughout the studies to capture all pressure drop profiles from the human volunteers and the Hydraulic Lung. It consists of a pressure transducer (Endevco 8507C-5) to detect the pressure drop across the device under test, an amplifier (CED 1902) to sense the pressure transducer and generate digital output and a laptop computer (IBM ThinkPad 600) to run the purpose-designed software which aquires, processes, displays and stores data from the amplifier.

Figure 3.5 The inhalation profile recorder and model device



3.3. The model device

The model device (Figure 3.6) was constructed from acetal. A screw-thread allows the two halves to be separated and a resistor disc inserted, as shown in Figure 3.7. The resistors were of the same material as the device, and accurately drilled with holes of 3.0, 4.5, 5.0, 6.0 and 7.0mm diameter. The device has a flush, right-angled pressure tap of 1.0mm diameter between the resistor and the mouthpiece which can be connected to the inhalation profile recorder. The resistivity of the device fitted with each of the five resistors was determined by measuring the pressure drop across the device at flow rates of 20, 40, 60 80 and 100 litres.minute^{-1}, and determining the slope of a linear regression line fitted to a plot of $\sqrt{\Delta P}$ against flow rate, in accordance with equation 1.1.

Figure 3.6 The model device

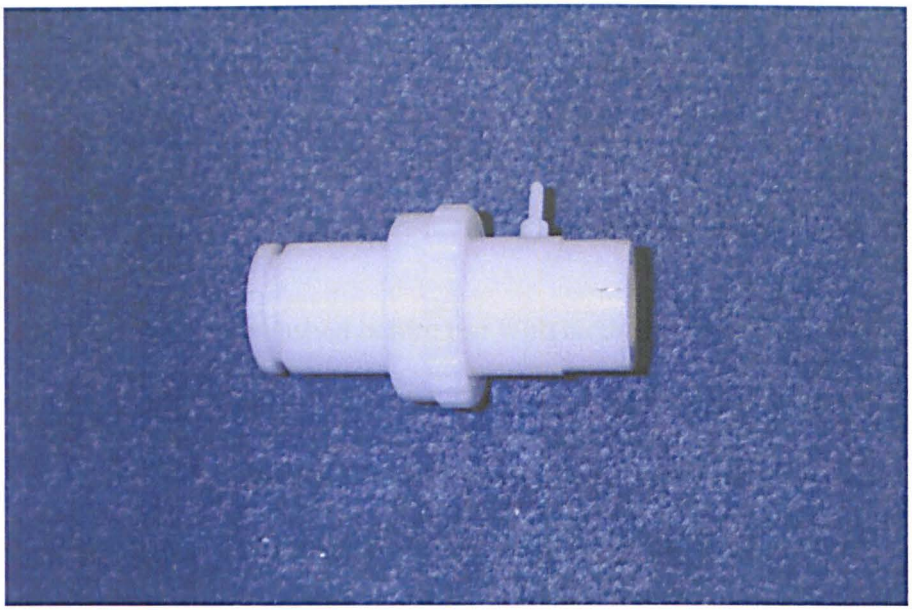
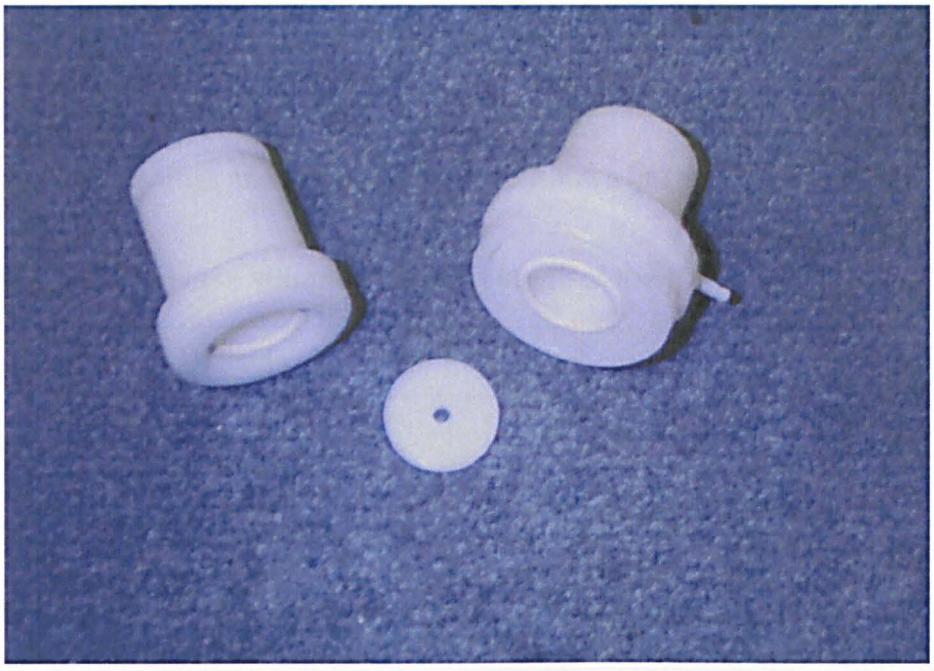


Figure 3.7 The model device and resistor



3.4. Particle penetration using the Multi-Stage Liquid Impinger (MSLI)

3.4.1. Use of the MSLI

The function of the MSLI (Copley Scientific Limited) is described in section 5.1.4. Operation of the MSLI in the particle penetration experiments was as follows:

Each stage of the MSLI was washed before use with methanol and allowed to dry at room temperature. A glass fibre filter (Gelman, A/E) was placed on the final stage and 20ml of dissolving solvent (70:30 methanol: water) was dispensed into each of stages 1 to 4. A standard USP right-angled throat was fitted to the inlet of the apparatus. The MSLI was connected either to a standard vacuum pump (Model HCP4, Copley Scientific Limited) or to the Hydraulic Lung. The DPI under test was fitted to the mouth of the USP throat with an airtight rubber mouthpiece. The inhalation profiles used for testing are described in section 5.1.5. The test DPI was actuated five times with the appropriate flow profile. Following dose collection each stage of the MSLI was rinsed three times with dissolving solvent and the washings made up to the volumes shown in Table 3.1.

Table 3.1 Total wash volumes for each stage of the MSLI

Stage	Volume (ml)
Throat and mouthpiece	250
Stage 1	250
Stage 2	250
Stage 3	200
Stage 4	100
Filter	50

Each analysis was performed in triplicate.

3.4.2. High Performance Liquid Chromatography (HPLC) analysis of salmeterol and fluticasone propionate

Drug deposition (for both salmeterol and fluticasone propionate) on each stage of the MSLI was determined using the following chromatographic conditions:

Column:	20cm x 4.6mm i.d. Hypersil BDS C_{18}
Mobile phase:	Methanol:acetonitrile:0.2M aqueous ammonium acetate containing 0.5%w/v tetrabutylammonium hydrogen sulphate (30:30:40 v/v)
Flow rate :	1.5 ml.minute^{-1}
Temperature	40^{o}C
UV detection:	228nm
Injection volume:	100ul
Run time:	~10 minutes

3.4.3. Test DPI

The product tested was Seretide Accuhaler 100/50 (GlaxoSmithKline plc, Ware, Hertfordshire) batch number B014835.

4. COMPARISON OF HUMAN AND HYDRAULIC LUNG INHALATION CHARACTERISTICS

4.1. Introduction

As described in Chapter 1, the principal purpose of the Hydraulic Lung was to explore the relationship between DPI resistivity, inspiratory effort and the characteristics of inhalation profiles, principally flow rate or pressure drop, but also flow acceleration rates. These relationships have also been explored to some extent in previous studies using data acquired from human subjects, but many human subjects find it difficult to reproduce a given level of inspiratory effort when using inhalers of varying resistivity. This is likely to result in a significant degree of uncertainty in relationships based on inspiratory effort derived from this data. The Hydraulic Lung, being mechanical, is highly reproducible, which should allow accurate determination of such relationships. However, the data generated by the Hydraulic Lung must be compared to human data to demonstrate equivalence within the level of experimental accuracy which can be achieved. It was therefore necessary to generate experimental designs for both Hydraulic Lung and human volunteer studies which would allow statistical comparison of the results.

In order to calculate and attempt to match the range of inspiratory efforts achieved by the human subjects it was necessary to establish the MIPs achieved by the Hydraulic Lung with varying levels of inspiratory effort. This was done using the same model device and 0.1mm diameter resistor used in the human volunteer studies. From this data eight levels of inspiratory effort were chosen (15, 20, 25, 30, 35, 40, 45 and 50cm water). Each effort

level was used to generate inhalation profiles, in duplicate, with the same five resistors fitted in the model device.

4.2. Experimental Design

4.2.1. Clinical Study

The human volunteer study was designed and conducted before the Hydraulic Lung study so that a realistic range of inspiratory efforts could be established for use in the latter. Twenty volunteers, both male and female, were selected in order to provide a range of data (previous clinical studies by Clark and Hollingworth (1993) and Olssen and Asking (1994) had used sixteen and ten human subjects respectively).

The study was a single-centre, single-blinded, 5-way crossover study conducted in two sessions. In the first session the subjects were trained to inhale through the model device with moderate resistivity. Once satisfactory technique had been established, the Maximum Inspiratory Pressure (MIP) achievable by each volunteer was measured, by inhaling at maximum effort through a resistor with very small diameter (0.1mm). Volunteers were given three attempts to achieve the highest pressure drop of which they were capable.

The second session was conducted one week after the first. For each volunteer, five different resistors (3.0, 4.5, 5.0, 6.0 and 7.0mm diameter) were used in randomised order, and duplicate inhalations were recorded for each level of resistivity.

4.2.2. Hydraulic Lung study

In order to calculate and attempt to match the range of inspiratory efforts achieved by the human subjects it was necessary to establish the MIPs achieved by the Hydraulic Lung with varying levels of inspiratory effort. This was done using the same model device and 0.1mm diameter resistor used in the human volunteer studies. From these data eight levels of inspiratory effort were chosen (15, 20, 25, 30, 35, 40, 45 and 50cm water). Each effort level was used to generate inhalation profiles, in duplicate, with the same five resistors fitted in the model device.

4.3. Clinical Study

4.3.1. Ethical approval

Before the human volunteer study could be conducted, ethical approval was sought and obtained from within GlaxoSmithKline R&D and from the East and North Hertfordshire Local Research Ethics Committee. The approval application and the patient information and consent document generated in accordance with the recommendations of the Ethics Committee are included as Appendix A.

4.3.2. Subject demography

All volunteers were non-smokers with no documented history of exercise induced asthma, an exacerbation of asthma or any respiratory condition. Subject demographics are summarised in Table 4.1 below.

Table 4.1 Summary of Subject demographics

	Male	Female
Number of subjects	11	9
Mean age in years (range)	35 (25-48)	32 (26-53)
Mean height in inches (range)	69 (66-74)	64 (61-70)

4.3.3. Human data

4.3.3.1. Range of inhalation characteristics observed and trends

The twenty subjects displayed a significant range of pressure drops, flow accelerations and inhaled volumes for each level of device resistivity, as shown in Table 4.2. The range for pressure drop and inhalation volumes was approximately five-fold, while that for flow acceleration was larger and highly variable.

Table 4.2 Range of inhalation characteristics achieved across twenty subjects

Resistor orifice diameter (mm)	Range of pressure drop values (kPa)	Range of flow acceleration values (litres.min.$^{-1}$.sec.$^{-1}$)	Range of inhalation volume values (litres)
3.0	2.51 – 12.67	54.84 – 421.20	0.69 – 4.01
4.5	1.79 – 11.23	48.46 – 3819.46	0.78 – 4.72
5.0	2.30 – 11.68	132.42 – 2214.06	1.17 – 5.25
6.0	1.56 – 10.21	88.52 – 6874.86	1.30 – 5.29
7.0	0.64 – 8.49	112.89 – 2500.77	1.49 – 5.12

It can be seen that both maximum and minimum pressure drop values tended to decrease with increasing resistor orifice diameter (lower resistivity), while inhaled volumes showed the opposite trend. This latter observation probably reflects the reasonable conclusion that it takes less effort to reach full lung capacity when inhaling against a low resistance. Trends within the flow acceleration values are not clearly evident in the maximum and minimum values. Examination of the full data set, however, shows higher flow acceleration values are associated with lower resistivity as might be expected. Peak Inspiratory Flow Rate (PIFR) values were calculated from the pressure drop data using a variation of equation 1.1.

$$PIFR = \sqrt{\Delta P}/R \text{ litres.minute}^{-1}$$

Where PIFR = peak inspiratory flow rate

ΔP = pressure drop

R = specific resistance, or resistivity

These values therefore reflect the ranges and trends observed for the pressure drops, with a square root relationship. Clark and Hollingworth (1992) measured PIFR values in healthy volunteers across a range of resistivity values and found that variability in PIFR increased with decreasing resistivity. This result was also observed in this study, as shown in Figure 4.1. When the data is plotted as pressure drop, rather than PIFR, it can be seen that variability in pressure drop is quite consistent as resistivity varies (Figure 4.2) and the effect in PIFR is a consequence of the relationship in equation 1.1; i.e. the smaller range of flow rates achievable with increased resistivity.

Flow acceleration follows the same pattern of variability as PIFR, as shown in Figure 4.3, but with some extreme outliers. Flow acceleration was determined manually from each inhalation profile by identifying the start and end points of the longest linear section of the profile before the peak pressure drop (or PIFR) was reached. The difference in flow rates between these two points was divided by the time interval between them. Some degree of subjectivity is involved in this procedure, partly due to the range of profile shapes between subjects, which may introduce some additional variation. Seven extreme outliers were apparent among the two hundred data points, where values significantly in excess of 1500 litres.minute^{-1}.second^{-1} were recorded (between 2000 and 7000 litres.minute^{-1}.second^{-1}). These outliers were found to occur in the profiles of two subjects, and may be due to a difference in inhalation technique. Very high flow accelerations might be achieved, for example, by expanding the chest as far as possible before opening the mouth to start the inhalation. These seven extreme flow acceleration values were excluded from the data analysis discussed in section 4.7.

Figure 4.1 PIFR and resistivity

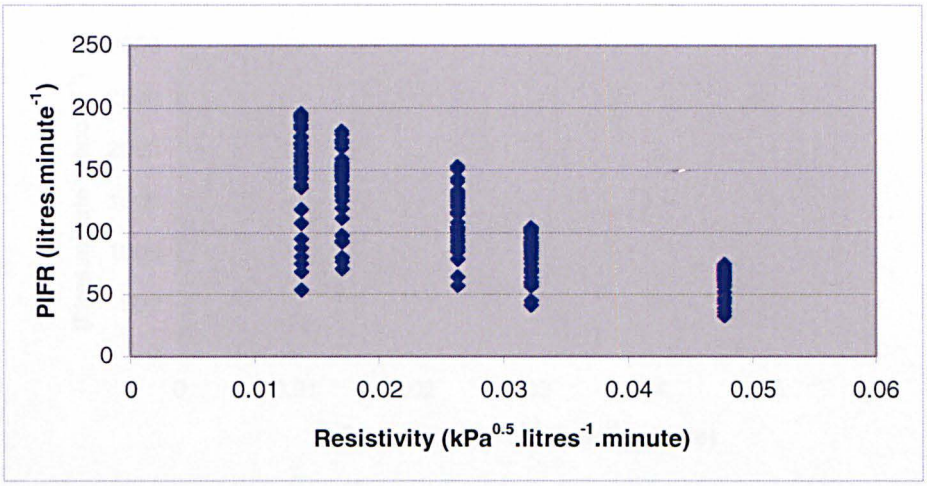


Figure 4.2 Peak pressure drop and resistivity

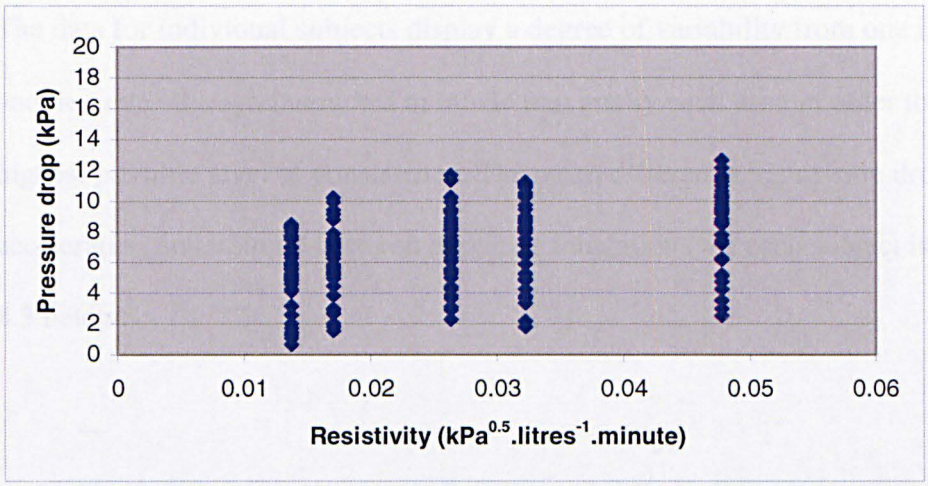
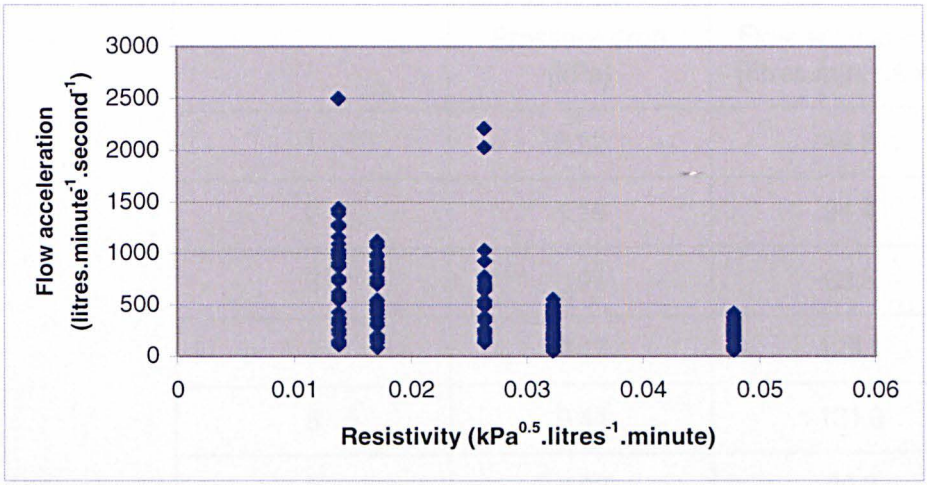


Figure 4.3 Flow acceleration* and resistivity



*Flow acceleration values above 3000 litres.minute^{-1}.second^{-1} are not shown

4.3.3.2. Within subject variability

The data for individual subjects display a degree of variability from one inhalation to another, even though instructed to inhale maximally each time in order to achieve the highest possible level of consistency. The mean difference in pressure drop, flow acceleration and volume between duplicate inhalations for each subject is shown in Table 4.3 below.

Table 4.3 Variability in inhalation measurements for human subjects

Subject	Mean difference between duplicate inhalations		
	Pressure drop (kPa)	Flow acceleration (litres.min.$^{-1}$.sec^{-1})	Volume (litres)
1	0.22	44.8	0.10
2	1.16	94.4	0.50
3	0.94	63.5	0.56
4	0.47	129.1	0.18
5	0.44	131.6	0.30
6	0.63	80.3	0.14
7	1.05	602.9	0.57
8	1.78	123.9	0.35
9	0.46	97.6	0.12
10	0.44	88.6	0.20
11	0.48	138.6	0.12
12	0.43	111.3	0.25
13	0.67	89.4	0.24
14	0.39	52.3	0.22
15	0.77	132.5	0.22
16	0.71	69.7	0.23
17	1.25	112.7	0.14
18	0.62	255.1	0.17
19	0.51	26.77	0.32
20	0.46	554.3	0.56
Overall mean	0.69	150.0	0.27

The shape of inhalation flow profiles varied between subjects. Examples (as flow profiles) of different profiles for low and high resistivity are shown in Figures 4.4 and 4.5.

Figure 4.4 Flow profiles for subject 8

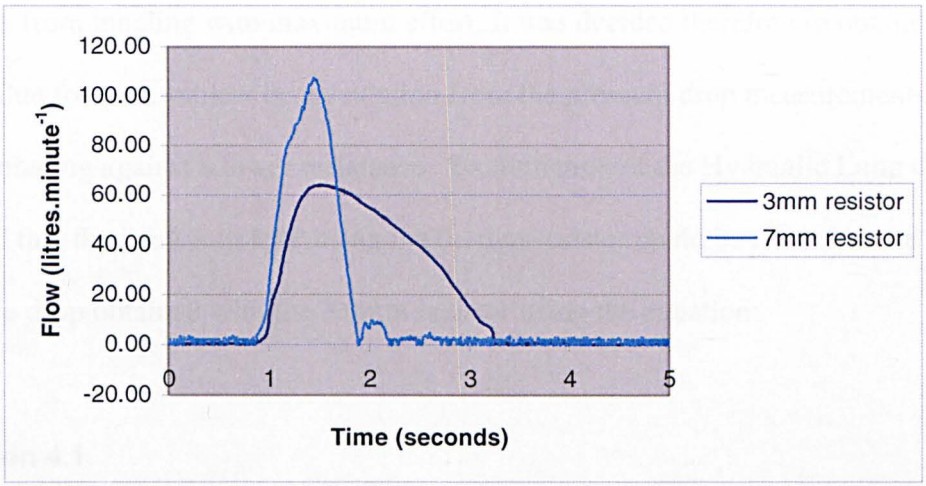
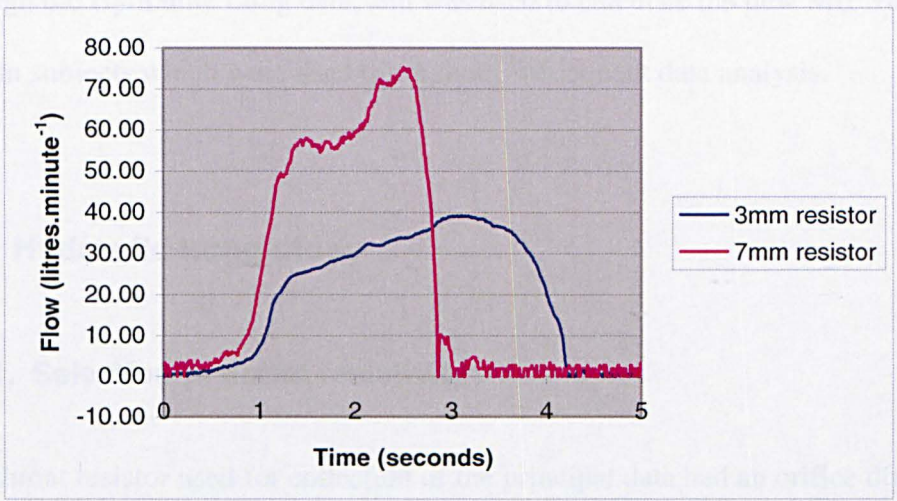


Figure 4.5 Flow profiles for subject 14



4.3.3.3. Maximum Inspiratory Pressure

The MIP values for each subject, determined by inhalation against a very high resistivity device, were found to be unreliable, since a significant number of the subjects (eight out of twenty) exceeded their MIP during inhalations with lower resistivity devices. This may be due to discomfort experienced when inhaling against very high resistances preventing subjects from inhaling with maximum effort. It was decided therefore to obtain a new MIP value for each subject by calculation from the pressure drop measurements made when inhaling against a lower resistance. Examination of the Hydraulic Lung data showed that the measured MIP using the 0.1mm resistor could be related to the peak pressure drop obtained with the 3.0mm resistor using the equation:

Equation 4.1

$$MIP = 1.154\Delta P + 0.5567 \text{ kPa}$$

This relationship was based on a linear regression (correlation coefficient, $R^2 > 0.999$) through the Hydraulic Lung data, and was used to calculate the new MIP values for the human subjects which were used throughout subsequent data analysis.

4.4. Hydraulic Lung study

4.4.1. Selection of throat resistivity

The throat resistor used for collection of the principal data had an orifice diameter of 9.6mm, such that the model device fitted with any of the five resistors was always the

point of greatest resistivity in the inhalation system. This throat resistor is representative of the minimum diameter of the laryngopharynx in a study of twenty human volunteers

examined by Magnetic Resonance Imaging (MRI) scanned whilst inhaling (data on file relating to McRobbie, 2003).

4.4.2. Hydraulic Lung data

4.4.2.1. Range of inhalation characteristics and trends

Ranges of observed values of pressure drop, flow acceleration and inhaled volume for each level of resistivity are shown in Table 4.4. Certain trends are evident in both maximum and minimum values, i.e. as resistivity increases (with decreasing resistor orifice diameter) pressure drop values increase and flow acceleration and inhaled volume values decrease.

Table 4.4 Range of inhalation characteristics achieved with Hydraulic Lung

Resistor orifice diameter (mm)	Range of pressure drop values (kPa)	Range of flow acceleration values (litres.min.$^{-1}$.sec.$^{-1}$)	Range of inhalation volume values (litres)
3.0	2.60 – 7.97	68.3 – 182.1	1.08 – 3.37
4.5	2.12 – 7.11	94.4 – 257.5	1.03 – 3.28
5.0	2.00 – 6.90	115.6 – 309.6	1.15 – 3.74
6.0	1.49 – 5.93	169.3 – 541.8	1.29 – 4.12
7.0	1.11 – 5.13	233 – 564.7	1.31 – 4.21

4.4.2.2. Variability between duplicate runs

The Hydraulic Lung was found to be highly reproducible. The mean difference between duplicate measurements was 0.02kPa for pressure drop, 7.9 litres.minute^{-1}.second^{-1} for acceleration and 0.02 litres for volume.

4.4.2.3. Human and Hydraulic Lung MIP values

The MIP values of the twenty human volunteers spanned the range 3.7 to 14.9kPa. The height of the water column in the Hydraulic Lung was varied between 15 and 50cm water to provide a range of MIPs from 3.5 to 9.7kPa. Higher levels of MIP needed to match the full range of human MIPs are not achievable in the current Hydraulic Lung, though redesign of the apparatus could be considered to address this problem.

4.5. Relationships derived from data

One of the key objectives of the present study was to use the Hydraulic Lung explore the relationship between DPI resistivity, inspiratory effort and the principal characteristics of inhalation profiles, i.e. pressure drop or flow rate, and flow acceleration. These relationships are preferably derived from the Hydraulic Lung data, which is highly reproducible, and then applied to the human data, which is less reproducible, to verify that they are equally applicable.

4.5.1. Resistivity, inspiratory effort and pressure drop

The most important relationship to establish for use in *in-vitro* testing of DPIs is that which relates the resistivity of a given device, a chosen level of inspiratory effort and the

resultant pressure drop across the device. Flow rate could, of course, be used in place of pressure drop. However, since inspiratory effort has been defined here as a pressure drop (the MIP) the relationship sought in this study may appear less complex using pressure drop rather than flow rate as the principal inhalation characteristic.

As described in section 4.4.2.1, certain relationships between inspiratory effort, resistivity and pressure drop are immediately apparent within the results:

- As resistivity increases pressure drop increases for a given level of inspiratory effort (Figure 4.6)
- As inspiratory effort increases pressure drop increases for a given level of resistivity (Figure 4.7)

Figure 4.6. Pressure drop versus resistivity

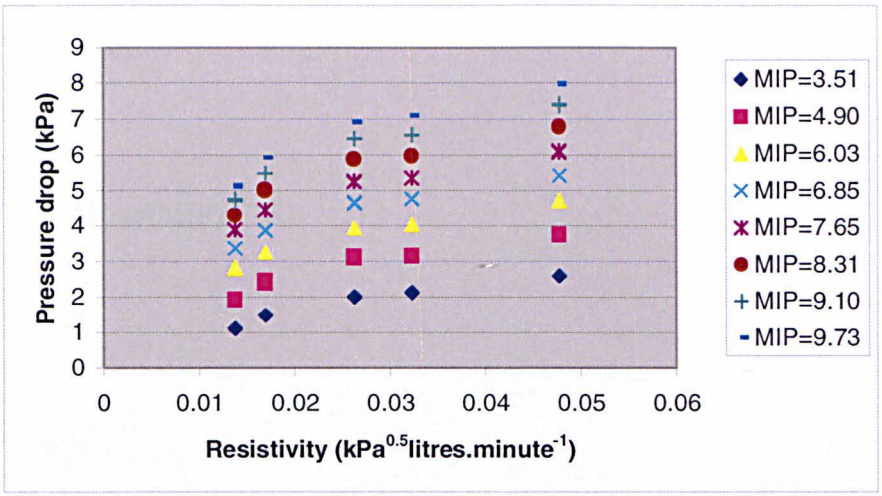
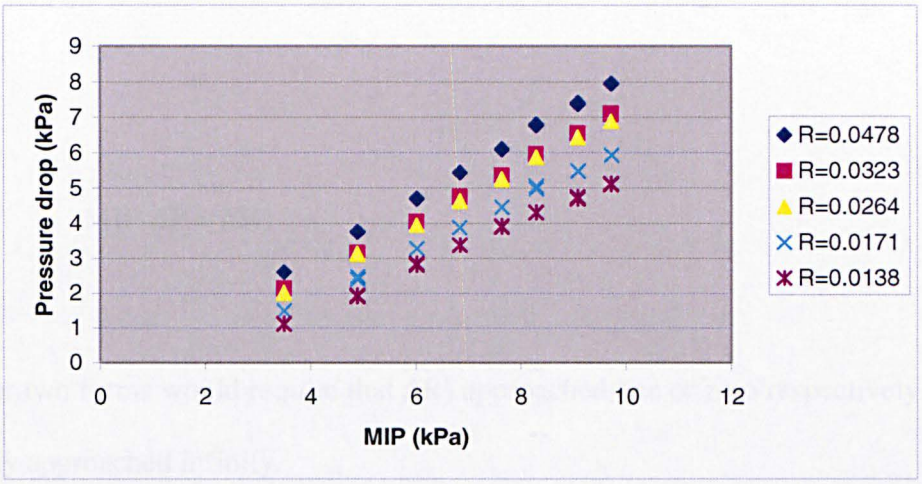


Figure 4.7. Pressure drop versus inspiratory effort (MIP)



The relationship between pressure drop and resistivity is clearly non-linear. The relationship between pressure drop and inspiratory effort is approximately linear but the regression line through each data set has a different slope and different intercept. Neither plot, therefore, suggests a simple equation which can relate inspiratory effort, resistivity and pressure drop.

The desired equation defining the relationship between all three factors could take the forms:

$$\Delta P = f(\text{MIP}).f'(\text{R})$$

Or:

$$\Delta P/\text{MIP} = f(\text{R})$$

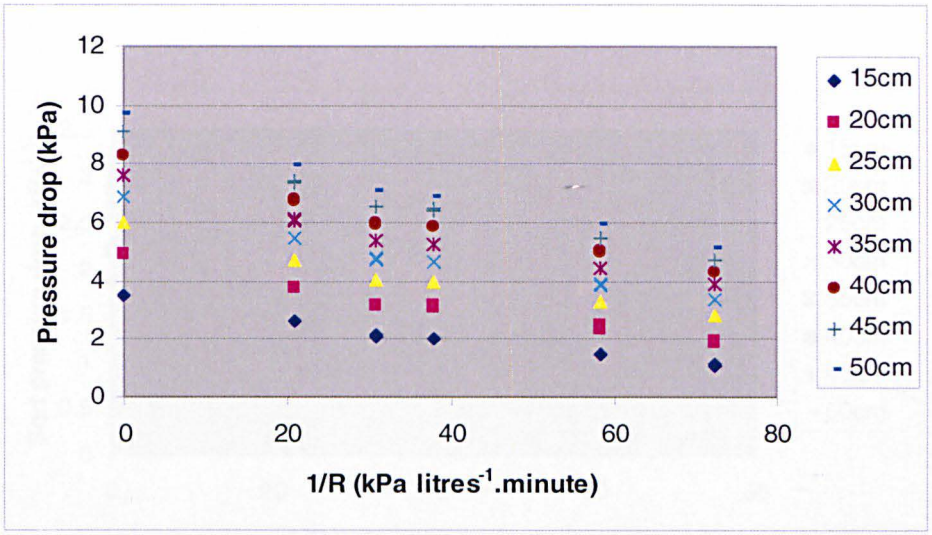
Or:

$$\text{MIP}-\Delta P = f(\text{R})$$

The latter two forms would require that $f(\text{R})$ approached one or zero respectively as resistivity approached infinity.

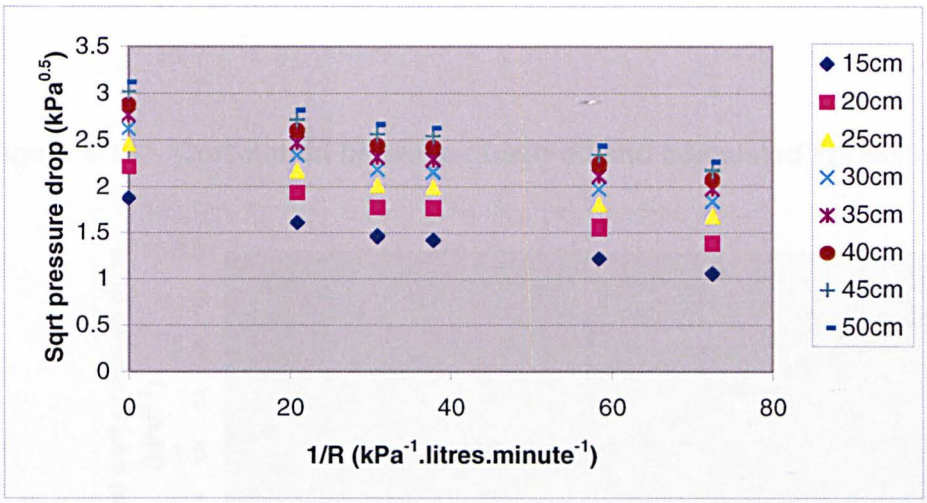
An improved approach to establishing a relationship between inspiratory effort, resistivity and pressure drop is to treat MIP as an additional value of pressure drop as resistivity approaches infinity. If pressure drop is plotted against the reciprocal of resistivity (1/R), MIP is the intercept where $1/\text{R} = 0$. The data plotted in this way (Figure 4.8) displays a gradual fall in pressure drop from the MIP as resistivity decreases.

Figure 4.8. Pressure drop versus reciprocal of resistivity



The data fit a 2nd order polynomial relationship but the relationship is slightly different for each level of inspiratory effort. It was found, however, that a plot of the square root of pressure drop against the reciprocal of resistivity gave a linear relationship, with intercept equal to the square root of MIP, and approximately the same slope (-0.011 $kPa^{0.5}$ / (kPa.$litres^{-1}$ .minute)) for each level of inspiratory effort (Figure 4.9).

Figure 4.9. Square root of pressure drop versus reciprocal of resistivity



The relationship between inspiratory effort, resistivity and pressure drop was therefore found to be described by the equation:

Equation 4.2

$$\sqrt{\Delta P} = \sqrt{MIP} - 0.011/R \qquad kPa^{0.5}$$

From equation (1.1):

$$PIFR = \sqrt{\Delta P}/R \qquad litres.minute^{-1}$$

Therefore:

Equation 4.3

$$Q = \sqrt{MIP}/R - 0.011/R^2$$

Correlations between calculated and observed values of √pressure drop and PIFR are shown in Figures 4.10 and 4.11.

Figure 4.10. Correlation between observed and calculated √pressure drop

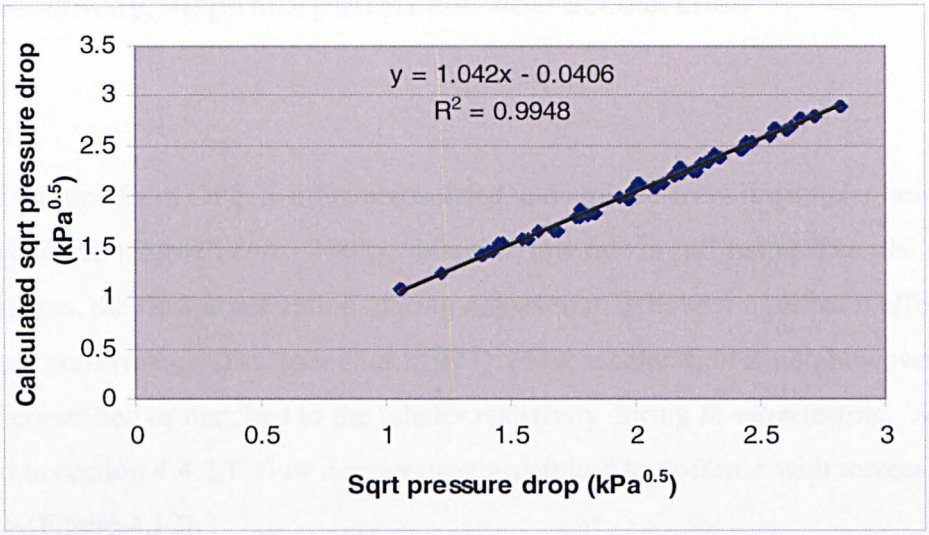
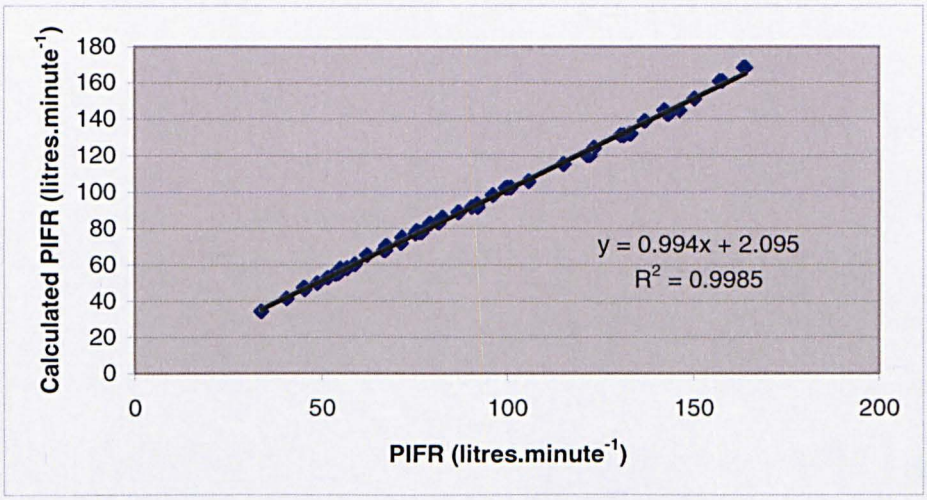


Figure 4.11 Correlation between observed and calculated PIFR

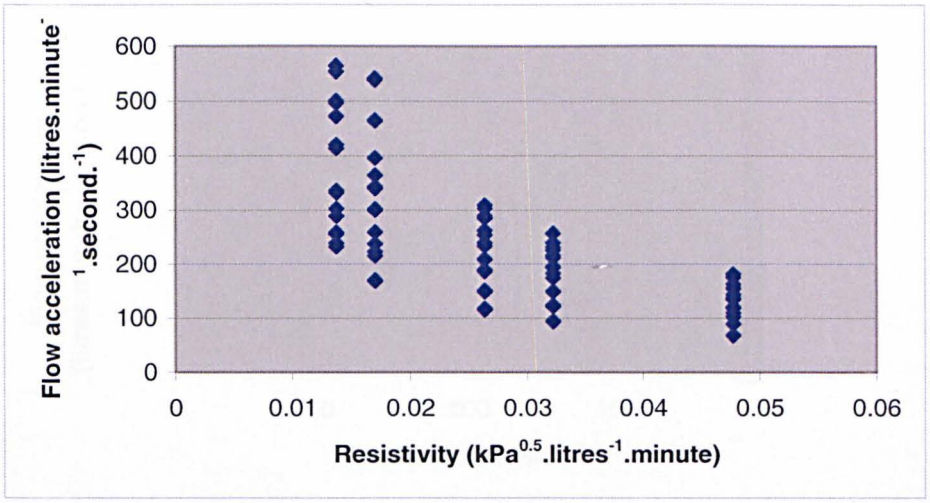


The correlation between observed and calculated √pressure drop for the Hydraulic Lung is good, with a correlation coefficient close to one ($R^2 > 0.99$) and intercept close to zero (equivalent to 0.002 kPa). The correlation for PIFR, as expected, is equally good ($R^2 > 0.99$, intercept = 2.1 litres.minute^{-1}).

4.5.2. Resistivity, inspiratory effort and flow acceleration

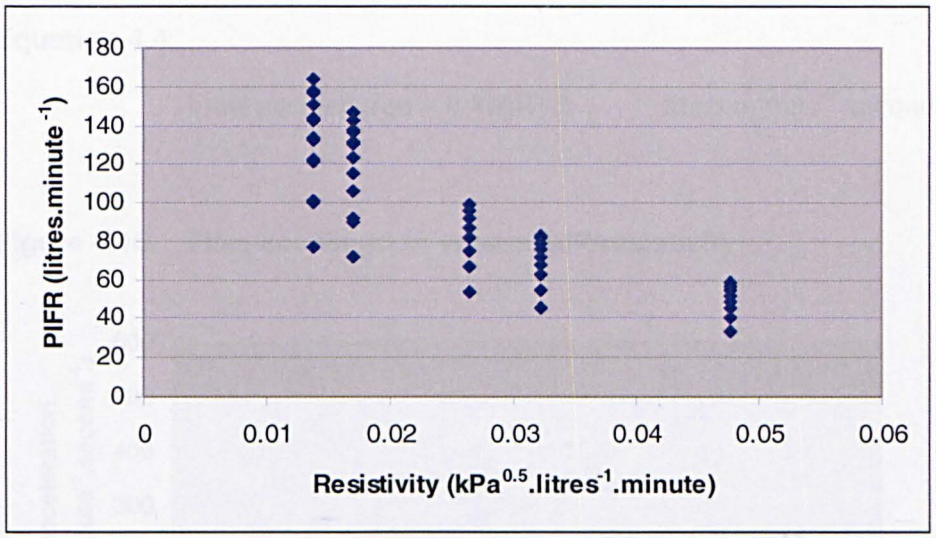
The dose emitted from DPIs is often aerosolised and emitted from the inhaler before the PIFR is achieved (Burnell *et al.*, 1998) while the flow rate is still rising. The rate at which flow increases, the flow acceleration, during emission may have a significant effect on the product performance (De Boer *et al.*. 1997). Flow acceleration is not, however, typically controlled or matched to the inhaler resistivity during *in-vitro* testing. As described in section 4.4.2.1, flow acceleration was found to decrease with increasing resistivity (Figure 4.12).

Figure 4.12. Flow acceleration versus resistivity



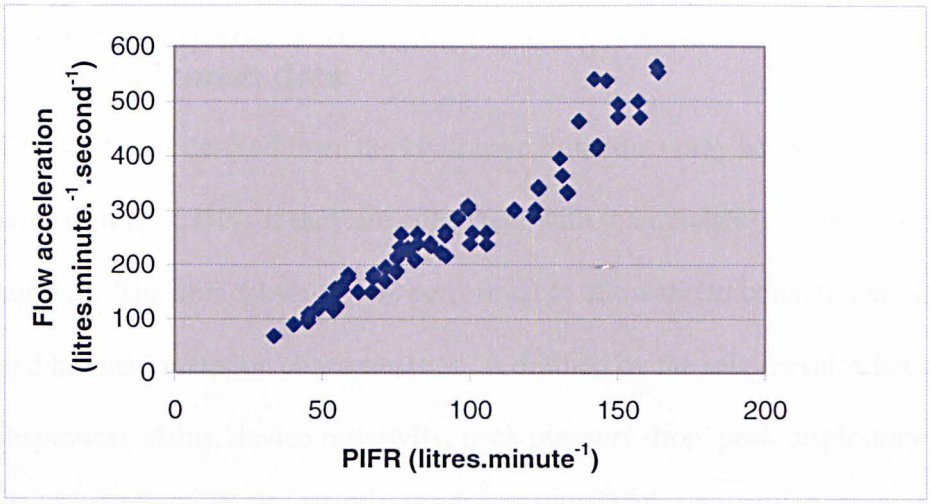
The behaviour of flow acceleration is similar to that of PIFR, shown in Figure 4.13.

Figure 4.13. PIFR versus resistivity



A correlation is therefore expected between flow acceleration and PIFR, i.e. the higher the PIFR the higher the flow acceleration. This correlation is demonstrated in Figure 4.14.

Figure 4.14. Flow acceleration versus PIFR

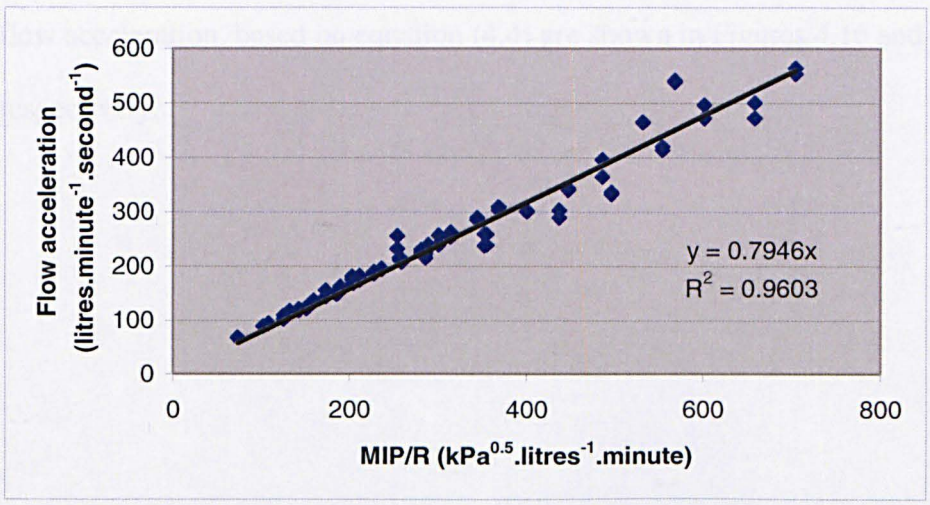


A better-correlated relationship was, however, found between flow acceleration, MIP and resistivity (Figure 4.15) which is approximately described by the simple relationship:

Equation 4.4

$$\text{Flow acceleration} = 0.8\text{MIP/R} \qquad \text{litres.minute}^{-1}\text{.second}^{-1}$$

Figure 4.15. Flow acceleration versus MIP/resistivity



4.6. Comparison of relationships derived from Hydraulic Lung data with human data

The equations derived from the Hydraulic Lung data may be usefully applied to the *in-vitro* testing of DPIs if they are consistent with the inhalation behaviour of human subjects. The clinical study was performed to allow direct comparison of Hydraulic Lung and human inhalation characteristics, as defined by the relationships between the inspiratory effort, device resistivity, peak pressure drop, peak inspiratory flow rate and flow acceleration.

Comparisons were performed by plotting the observed human data against calculated values based on the equations, and fitting a linear regression. The slope of such a regression should be close to unity, and the intercept close to zero if there is agreement between the two sets of data. Since there is significant scatter in the human data, statistical confidence limits (95%) were applied to the regression.

Plots of observed and calculated values of pressure drop, based on equation (4.2) and flow acceleration, based on equation (4.4) are shown in Figures 4.16 and 4.17 respectively.

Figure 4.16. Observed versus calculated values of √pressure drop for human subjects

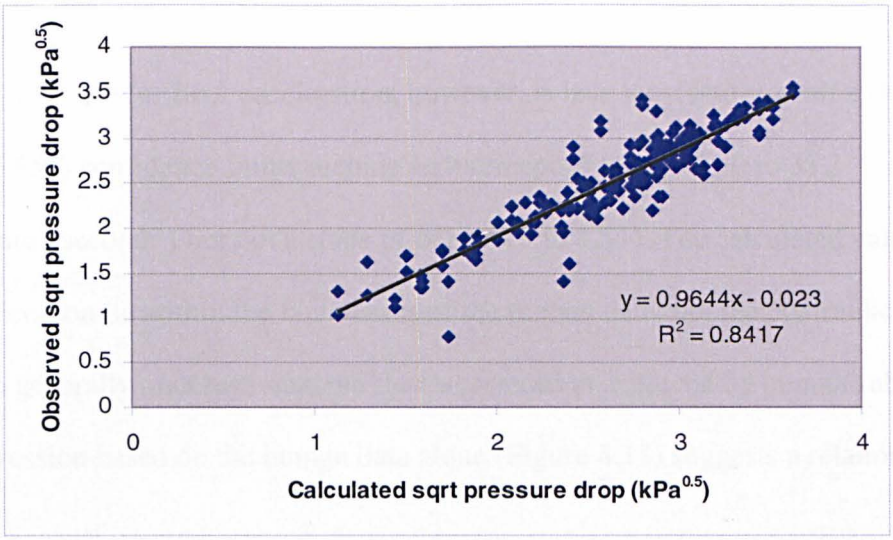
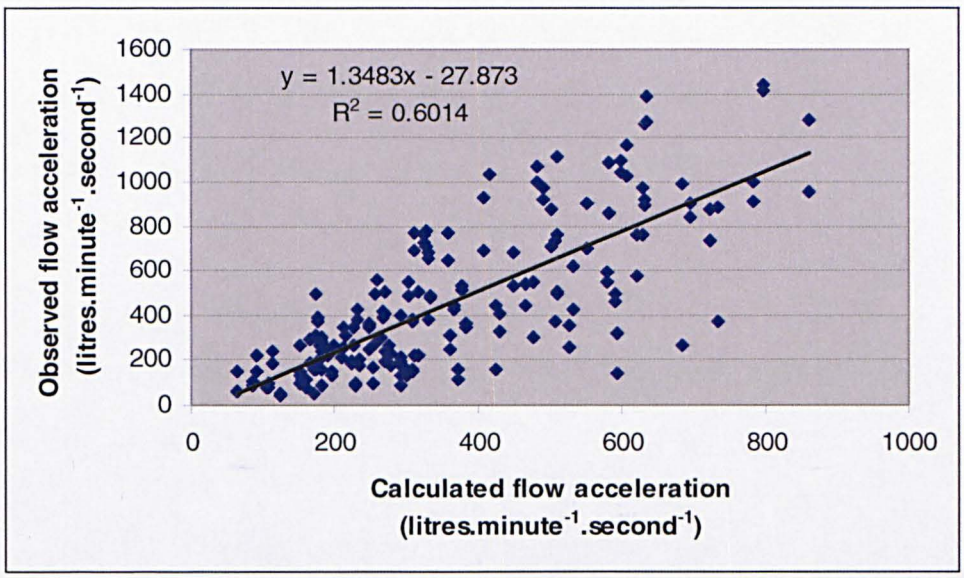


Figure 4.17. Observed versus calculated values of flow acceleration for human subjects



The regression line for √pressure drop appears to fit the human data well. The calculated confidence limits include an intercept of zero (-0.18 to 0.14 $kPa^{0.5}$) and a slope of one

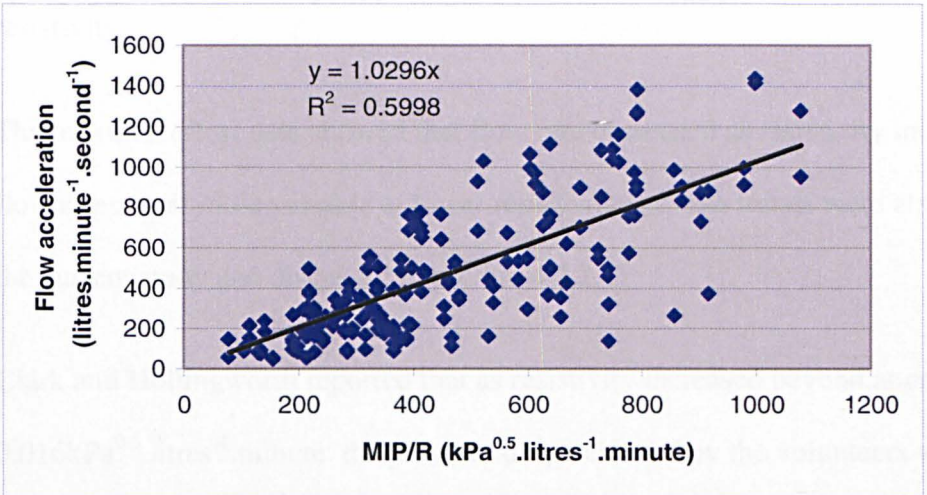
(0.91 to 1.02) demonstrating no significant difference between the two sets of data at this level of confidence.

The regression line for flow acceleration, however, is less satisfactory, with a slope of 1.35. The 95% confidence limits include an intercept of zero (-91.0 to 35.3 litres.minute^{-1}.second^{-1}) but not a slope of one (1.19 to 1.51). The calculated values for flow acceleration lie within the boundaries of the human data, but the Hydraulic Lung appears to generally underestimate the flow acceleration achieved by human subjects. A linear regression based on the human data alone (Figure 4.18) suggests a relationship closer to:

Equation 4.5

$$\text{Flow acceleration} = 1.03MIP/R \qquad \text{litres.minute}^{-1}\text{.second}^{-1}$$

Figure 4.18. Flow acceleration versus MIP/resistivity for human subjects



4.7. Comparison of findings with those of other studies

The relationship between DPI resistivity and peak inspiratory flow rates in humans has been studied by other researchers in order to apply the findings to *in-vitro* testing; most notably Clark and Hollingworth (1993) and Olsson and Asking (1994).

4.7.1. Comparison of findings with those of Clark and Hollingworth

Clark and Hollingworth determined the specific resistance (termed resistivity in this work) for a number of commercial DPIs; plotting flow rate against the pressure drop developed across the device to verify a linear relationship as predicted by equation 1.1.

In order to extend the range of resistivities available for clinical study, they also manufactured a series of simple flow resistors with varying orifice diameters. The clinical

study was conducted with sixteen healthy volunteers and inhalations were recorded for the range of resistivities at both maximal and 'comfortable' effort levels. The 'comfortable' effort level data subsequently showed relatively poor correlation with resistivity.

The maximal effort data showed that flow rate decreased as resistivity increased, and that flow rates were more variable at lower resistivities. These trends were also observed in the current study and discussed in section 4.4.2.1.

Clark and Hollingworth reported that as resistivity increased beyond approximately $0.016 kPa^{0.5}.litres^{-1}.minute$ the pressure drop achieved by the volunteers was found to plateau at approximately 80cm H_2O (7.85kPa). They concluded that this might be the maximum negative pressure sustainable by the diaphragm and intercostal muscles. This finding was not observed in the current study, either for the human subjects or the Hydraulic Lung. In the current study, pressure drops were found to vary considerably from one subject to another, many exceeding 7.85kPa (the maximum recorded value was 12.67kPa) and increasing throughout the range of resistivities examined (0.0138 to $0.0478 kPa^{0.5}.litres^{-1}.minute$). For individual subjects, and for each level of effort in the Hydraulic Lung, a plot of pressure drop against resistivity did, however, display a gradually flattening curve. This curve would be expected to reach a maximum value equal to the MIP for that individual subject, or effort level, as resistivity increased. It would not be expected to reach a common value for all subjects. It is possible that the healthy volunteers in the Clark and Hollingworth study were all of similar capability in terms of inhalation.

Clark and Hollingworth's proposed formula for determining the appropriate flow rate for *in-vitro* testing of DPIs was based in part on the maximum pressure drop described above and also on the typical airways resistivity of the lungs determined for the volunteers. This latter value was calculated from the inhalation profile data using a relationship based on the conservation of volumetric flow. If the resistance offered by the lung and/or airways is considered to be in series with the resistance offered by the device, as shown in the diagram in Figure 4.19, and flow (Q) into the device is considered to be equal to the flow into the lungs, then:

Equation 4.6

$$Q = \sqrt{\Delta P_L}/R_L = \sqrt{\Delta P_D}/R_D = \sqrt{\Delta P}/R \quad \text{litres.minute}^{-1}$$

Where the combined resistivity is:

Equation 4.7

$$R = \sqrt{(R_L^2 + R_D^2)} \qquad kPa^{0.5}.litres^{-1}.minute$$

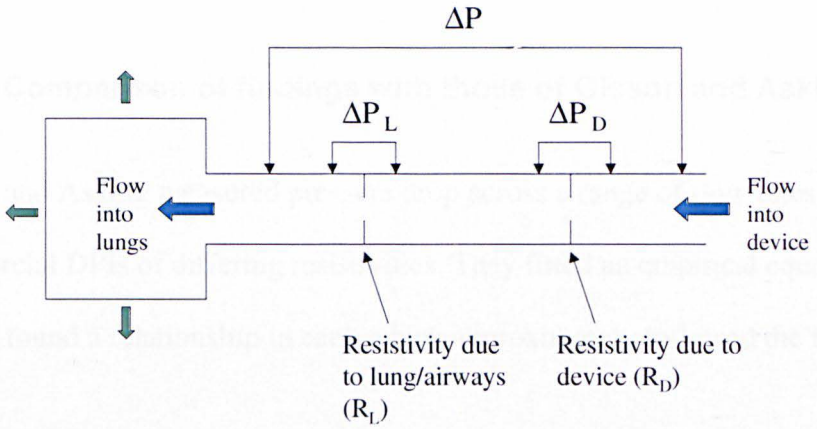
Rearrangement gives:

Equation 4.8

$$1/Q^2 = R_D^2/\Delta P + R_L^2/\Delta P \qquad litres^{-2}.minute^2$$

A plot of $1/Q^2$ against R_D^2 therefore gives a gradient equal to $1/\Delta P$ and an intercept equal to $R_L^2/\Delta P$. Hence, the lung's maximum pressure drop and the lung or airway resistivity can be found.

Figure 4.19. Lung/airways and device resistivities in series



The lung resistivity was calculated in this manner for each of the subjects in the current study. The mean lung resistivity of the twenty subjects was found to be 0.014 $kPa^{0.5}.litres^{-1}.minute$, with a range of 0.008 to 0.027 $kPa^{0.5}.litres^{-1}.minute$. This value is approximately twice as high as the average lung resistivity reported by Clark and Hollingworth, 0.007 $kPa^{0.5}.litres^{-1}.minute$. The Hydraulic Lung data were also plotted so that the calculated 'lung' resistivity could be compared with the known resistivity of the 'throat' resistor, which is placed in series with the device, just as shown in Figure 4.19 The calculated value was 0.0136 $kPa^{0.5}.litres^{-1}.minute$; approximately twice as high as the true value for the 9.57mm diameter orifice of 0.0071 $kPa^{0.5}.litres^{-1}.minute$. The discrepancy may occur because the assumption that the flow into the device and the flow into the 'lung' have equalised is not correct at the point when the peak pressure drop is

recorded, typically within 0.5 seconds of the start of the inhalation. This could be tested by introducing a pressure tap into the Hydraulic Lung between the throat resistor and the falling column of water so that $\sqrt{\Delta P_L}$ and $\sqrt{\Delta P_D}$ could be recorded simultaneously.

4.7.2. Comparison of findings with those of Olsson and Asking

Olsson and Asking measured pressure drop across a range of flow rates for seven commercial DPIs of differing resistivities. They fitted an empirical equation to each data set and found a relationship in each which approximately followed the form:

Equation 4.9

$$\Delta P = C.Q^{1.9} \quad \text{Pa}$$

where C is the proportionality coefficient, numerically equivalent to the pressure drop at 60 litres.minute^{-1} (one litre.second^{-1}). It is clear that this relationship is very similar to a form of equation 1.1,

Equation 4.10

$$\Delta P = R^2.Q^2 \quad \text{Pa}$$

Making C somewhat akin to R^2, or more accurately

Equation 4.11

$$C = R^2.Q^{0.1} \quad \text{Pa.litres}^{2.1}\text{.second}^{-2.1}$$

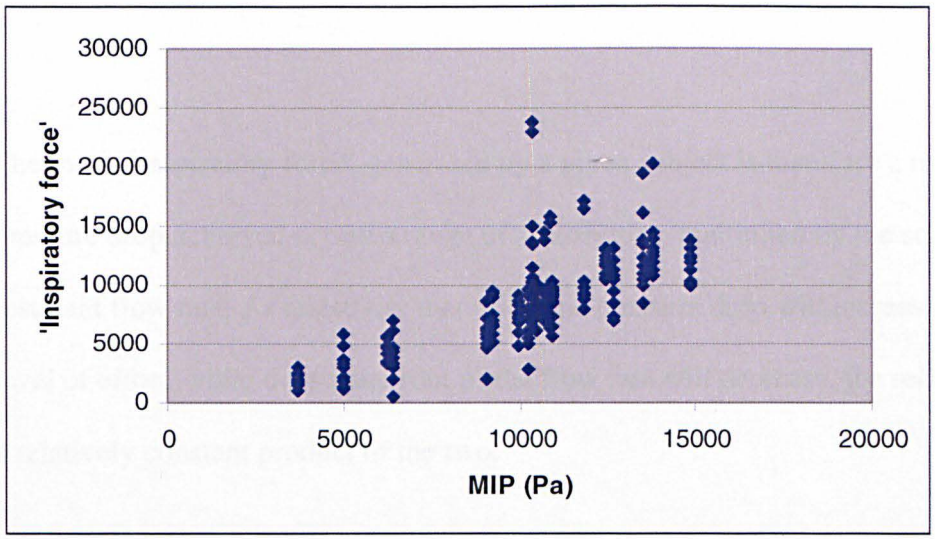
They then collected inhalation profiles, measuring flow rate, for ten healthy subjects inhaling with maximal effort through a series of resistors. An empirical model was again fitted to the data and the following relationship established:

Equation 4.12

$$K = C.Q^{2.4} \qquad Pa.second^{-0.5}.litres^{0.5}$$

Where K, termed the 'inspiratory force' (though not a true force) was a constant for each individual subject. Fitting human data from the current study to this equation, it was found that calculating the mean 'inspiratory force' for each subject ranked the subjects in approximately the same order as MIP, though the relative standard deviation for K within each subject was quite high (mean rsd = 24.6%). A plot of K against MIP is shown in Figure 4.20.

Figure 4.20. Correlation of 'inspiratory force' and MIP for human subjects



The range of values observed for K was 2028 to 14183 Pa.second$^{-0.5}$.litres$^{0.5}$ which appears to be in good agreement with Olsson and Asking, who did not publish the range of K values they obtained, but defined weak and strong inspiratory force values as 2200 and 12000 Pa.second$^{-0.5}$.litres$^{0.5}$ respectively.

Using equation 1.1 it can be seen that:

Equation 4.13

$$K = C.Q^{2.4} = R^2.Q^{0.1}.Q^{2.4} = R^2.Q^{2.5} \quad \text{Pa.second}^{-0.5}.\text{litres}^{0.5}$$

From equation 1.1:

$$\Delta P = R^2.Q^2 \quad \text{Pa}$$

Therefore:

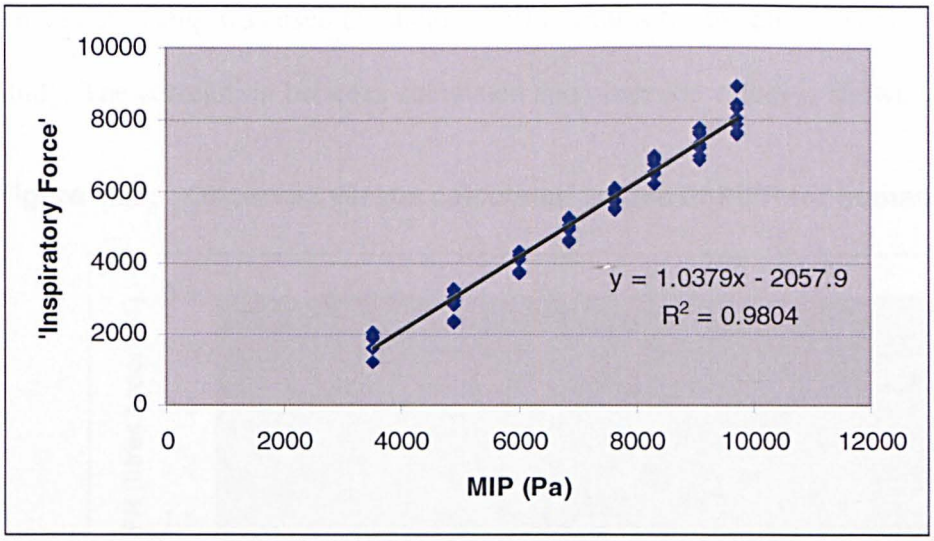
Equation 4.14

$$K = \Delta P.Q^{0.5} \quad Pa.second^{-0.5}.litres^{0.5}$$

The mean 'inspiratory force' generated by a given subject is therefore a measure of the pressure drop achieved across a range of resistivities, multiplied by the square root of the resultant flow rate. As resistivity increases, the pressure drop will increase for a given level of effort, while the square root of the flow rate will decrease, the relationship giving a relatively constant product of the two.

Values of 'inspiratory force' calculated for the Hydraulic Lung data demonstrate a strong linear correlation with MIP values, as shown in Figure 4.21.

Figure 4.21. Correlation of 'inspiratory force' and MIP for Hydraulic Lung data



This correlation allows an alternative relationship between flow rate, MIP and resistivity to be stated (using Olsson and Asking's chosen units, Pascals, litres and seconds):

Equation 4.15

$$K = 1.04MIP - 2058$$

Therefore since:

Equation 4.16

$$K = R^2.Q^{2.5}$$

Then:

Equation 4.17

$$R^2.Q^{2.5} = 1.04MIP-2057$$

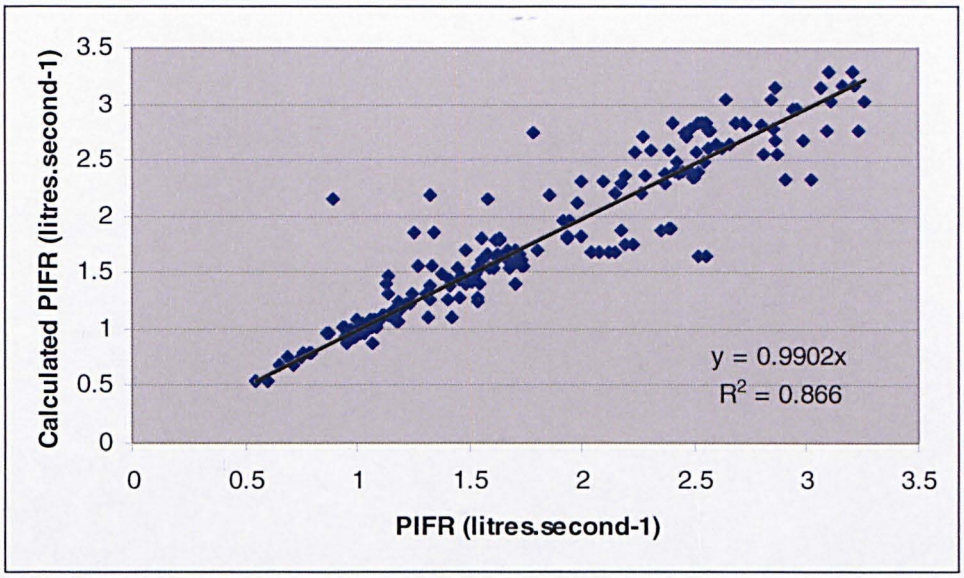
Rearranging:

Equation 4.18

$$Q^{2.5} = (1.04MIP - 2057)/R^2$$

This relationship was used to calculate PIFR values for the human subjects in the current study. The correlation between calculated and observed values is shown in Figure 4.22.

Figure 4.22. Observed versus calculated values of PIFR for human subjects



A linear regression (with intercept equal to zero) has a slope of 0.99 demonstrating good agreement between observed and calculated values.

Equation 4.18, therefore, could be used to calculate the appropriate flow rate for testing a DPI of known resistivity with a given level of inspiratory effort in place of equation 4.3, if desired.

4.8. Implications for *in-vitro* testing of DPIs

4.8.1. Selection of appropriate inspiratory effort

A simple relationship has been established which allows the appropriate pressure drop (or flow rate) for testing a DPI of known resistivity to be calculated at any desired level of inspiratory effort. This approach to choosing test conditions will allow comparative testing of different devices on a more realistic basis. However, it is necessary for an appropriate level or levels of inspiratory effort, represented by MIP, to be applied. Fortunately, MIP values for different patient groups are well documented in the literature (e.g. Wilson *et al.*, 1984; Harik-Khan *et al.*, 1998; Broeders, 2004; Aldrich and Spiro, 1995; Carpenter *et al.*, 1999) and appropriate levels of inspiratory effort could be proposed for standardised testing based on these for the desired target population. Alternatively, a similar approach to Olsson and Asking (1994) for weak, medium and strong inspiratory efforts could be applied.

4.8.2. Implications for particle sizing

Determination of the particle size distribution of the drug emitted from a DPI is commonly performed using an impactor such as the Andersen Cascade Impactor (May, 1945), or more recently the Next Generation Impactor (Marple *et al.*, 2003). Alternatively a liquid impinger such as the Twin Impinger (Hallworth and Westmoreland, 1987) or Multi Stage Liquid Impinger (May, 1966) may be used. Accurate particle size determination using these types of apparatus requires a constant, known flow rate as the

particles pass through the various cut-off stages, since air velocity determines the size of particles captured below each air jet. If DPIs are tested at different flow rates, it is necessary to recalculate the cut-off values for each stage of the apparatus in order to generate a size distribution. The equations for these calculations are well established and are already applied in the current pharmacopoeial recommendations for testing devices at a constant pressure drop of 4kPa (British Pharmacopoeia, 2002). Adoption of a new system for the choice of test flow rates would not, therefore, present a difficulty in this respect.

4.8.3. Application of realistic flow accelerations

The relationship between inspiratory effort, device resistivity and flow acceleration established for the Hydraulic Lung was not found to accurately reflect the relationship observed in the clinical study, though for purposes of practical applications of the Hydraulic Lung (discussed in Chapter 5) the acceleration values achieved were not unrealistic. However, for generalised testing of DPIs the simple relationship observed for human subjects (equation 4.5) could be applied. To date, it has not been typical practice to control flow acceleration during *in-vitro* testing in this way. This may in part be due to the practical difficulties involved in controlling flow acceleration without highly expensive equipment such as the Electronic Lung (Brindley *et al.*, 1994). However, the development of significantly cheaper computer-controlled pressure feedback pumps is likely to result in greater availability of the necessary equipment. A second difficulty with the application of varying flow acceleration rates during particle sizing is the potential effect on the effective cut-off diameters of any stages reached by the drug particles while the flow is still rising. This may necessitate the introduction of a 'buffer volume' between

the device and the first sizing stage to allow the desired test flow rate to be achieved before particles arrive there. If required, a maximum buffer volume could be calculated for a standardised flow acceleration range and applied to all apparatus. Although this may require some degree of redesign it would introduce a control which is not currently applied to ensure that particle sizing is not affected by transient flow rates through the test apparatus.

4.8.4. Conclusion

A standardised approach to the selection of more realistic pressure drops or flow rates for comparative testing of DPIs could be applied with currently available equipment and information. Further sophistication in terms of more realistic flow acceleration rates is also achievable with equipment which is now becoming more widely available.

5. APPLICATIONS OF THE HYDRAULIC LUNG AS A PRACTICAL TOOL FOR DPI TESTING

5.1. Drug penetration in an impinger

5.1.1. Introduction

The principal *in-vitro* test applied to DPIs is the measurement of the particle size distribution of drug delivered from the inhaler. This is a vital test because it can indicate the ability of the inhaler to deliver drug to the site of action within the lungs. The fraction of the dose comprising particles below approximately 6 microns in diameter is often referred to as the 'Respirable Dose' or 'Fine Particle Mass', and this may form part of the release test specification for the marketed product. It is not unusual for sub-components of the Respirable Dose, e.g. the fraction of particles between 3 and 4 microns to also form part of the release specification for more recently marketed products. The justification for specifications which control the sub-parts of a single dose is based on the knowledge that particles below 2 microns in size, for example, are likely to penetrate to peripheral areas of the lungs while those greater than 4 microns are more likely to deposit in the central airways (Johnson, 1998) A significant change in the proportion of particles in these size ranges might affect both the exposure of the patient to systemic side effects and the efficacy of the medication (Zanen, 1998).

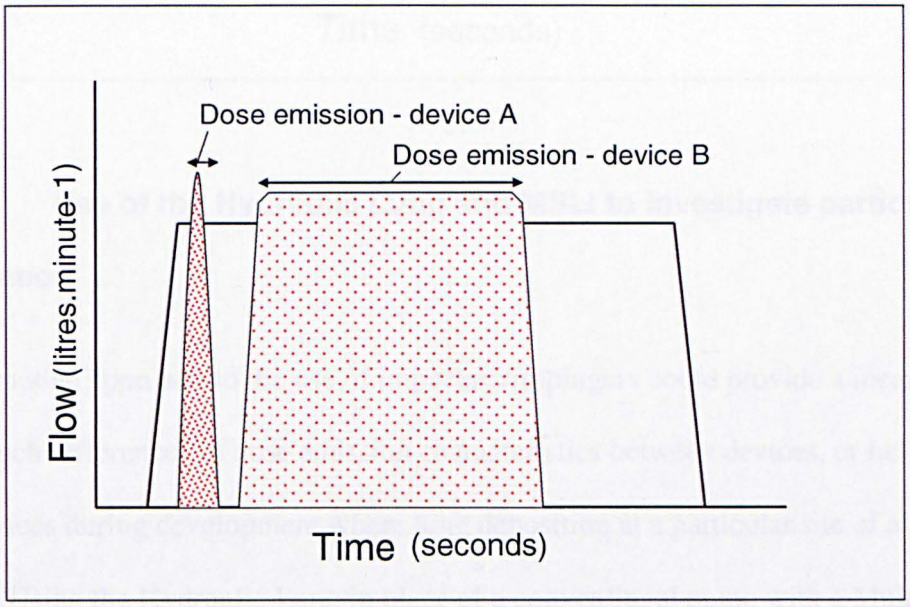
5.1.2. Flow profiles used in testing and effects on deposition

As described in Chapter 1, the test is typically performed using a multi-stage cascade impactor or liquid impinger, operated at a constant flow rate in order to obtain specific cut-off sizes at each impaction/impingement stage and hence allow the size distribution to be determined. To perform the test, air is drawn through the inhaler and impactor with a 'square' flow profile, i.e. the flow rate goes from zero to (typically) 60 litres/minute very rapidly then remains at 60 litres/minute for 3 or 4 seconds when it drops back to zero almost instantaneously. This type of flow profile is necessary to provide specific size cut-off values at each stage necessary for accurate sizing of the particles, but is clearly unrepresentative of patient inhalations, which generally show linear acceleration to a momentary peak flow and a gradual drop back to zero. A key disadvantage of the 'square' flow profile is that it may fail to differentiate between DPIs with different dose emission characteristics. This is illustrated in a theoretical example in Figure 5.1. If two DPI devices are compared where device 'A' emits it's dose, or cloud of aerosolised particles, early in the inhalation profile, while device 'B' emits it's dose throughout much of the inhalation profile, both particle clouds will encounter the cut-off points throughout the impactor at a flow rate of 60 litres/minute. If the particle size distributions of the two aerosol clouds are identical, the distribution patterns within the impactor will be identical, because the same sizing process will have taken place. This result is unrepresentative of the clinical situation, where use of the two DPI devices might result in different deposition patterns within the airways and consequently different clinical effects.

The particles emitted from device 'A', when inhaled by a patient, have the potential, if small enough, to be carried deep into the lung because they are contained within the

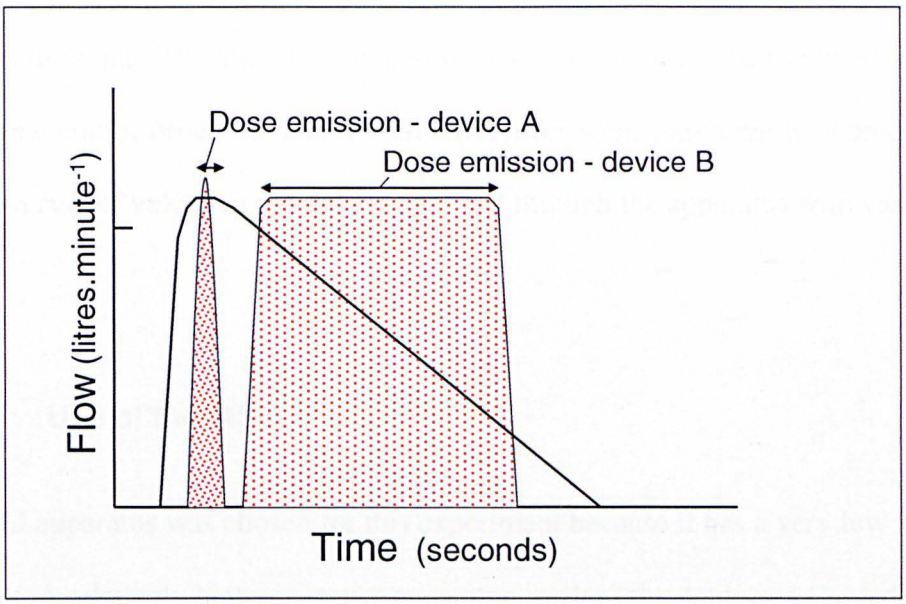
initial volume of air inhaled. Some of the particles emitted from device 'B' also have the potential to penetrate deeply, but those emitted towards the end of the inhalation may only penetrate into the upper airways, whatever their size, because the lung will have largely filled with air before they enter the respiratory system. This effect is the basis of bolus delivery of inhaled drugs (Bennett, 1991). The bolus is the portion of the inhaled volume which contains the drug. The bolus approach has been used in a number of studies where delivery of a drug has been targeted at a specific lung region in order to maximise therapeutic effect or reduce side-effects.

Figure 5.1 Dose emission from two theoretical DPIs with test profile



In addition to the effects of volume on the particle's ability to penetrate the lungs, the point of dose emission will also affect the flow rate at which particles encounter the 'cut-off' points within the respiratory system, since the flow rate in a typical human inhalation is constantly changing. This is illustrated in Figure 5.2

Figure 5.2 Dose emission from two theoretical DPIs with human profile



5.1.3. Use of the Hydraulic Lung and MSLI to investigate particle penetration

An alternative approach to the use of impactors/impingers could provide a means to detect such differences in dose emission characteristics between devices, or help optimise new devices during development where lung deposition at a particular site of action is desired. Using the Hydraulic Lung in place of a conventional pump with a Multi-Stage Liquid Impinger (MSLI), a human-like inhalation profile can be drawn through the apparatus instead of a conventional square flow profile. The flow rate will constantly change, with the result that emitted particles will experience impingement conditions at each successive stage which are dependent on their point of emission within the profile. The test is intended to measure particle penetration into the apparatus rather than particle size.

An experiment was conducted to compare the deposition patterns within a MSLI from a DPI using both conventional square flow profiles and human-like profiles generated by the Hydraulic Lung. The aim of the experiment was to establish if differences in deposition could be observed, and if such differences were consistent with predicted changes in cut-off values as the dose progressed through the apparatus with varying flow rate.

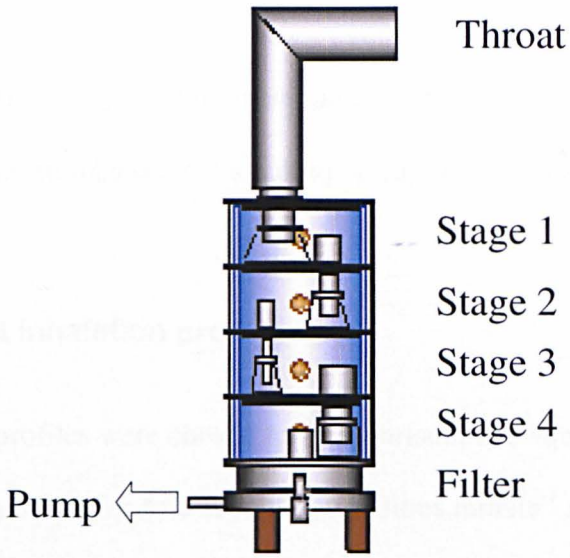
5.1.4. Use of the MSLI

The MSLI apparatus was chosen for this experiment because it has a very low inherent resistivity. A relatively high resistance apparatus, such as the Andersen Cascade Impactor, between the Hydraulic Lung and the DPI would significantly affect the inhalation profile.

The MSLI separates the aerosolised cloud of particles emitted from an inhaler into six stages (Figure 5.3); material is deposited on:

- The throat
- Stage 1
- Stage 2
- Stage 3
- Stage 4
- The filter

Figure 5.3 The Multi-Stage Liquid Impinger



The throat is a right-angled tube intended to represent the human throat and capture particles with high inertia; typically those of large, non-respirable size. Stages 1 to 4 are liquid impingement stages with the effective exit cut-off diameters (in microns) shown in Table 5.1, when operated at constant flow rates (Astra Draco Multi-Stage Impinger Instruction Manual, Copley, 1998)

Table 5.1 Effective cut-off diameters in the MSLI

	30 litres.minute^{-1}	60 litres.minute^{-1}
Stage 1	>9.6	>6.8
Stage 2	9.6	6.8
Stage 3	4.4	3.1
Stage 4	2.4	1.7

Effective cut-off diameters at other flow rates can be calculated using a variation of the Stoke's equation (Van Oort, 1996) :

Equation 5.1

$ECD_2=ECD_1 \times (Q_1/Q_2)^{1/2}$

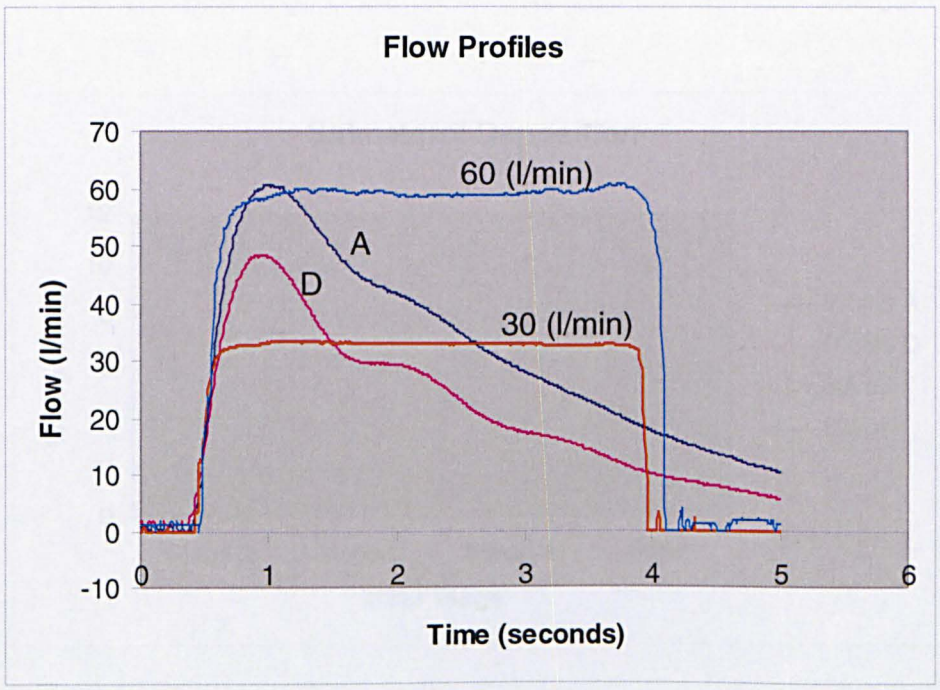
Where ECD = effective cut-off diameter and Q = flow rate.

The filter captures all material too small to be captured on Stage 4.

5.1.5. Test inhalation profiles

Four inhalation profiles were chosen for comparison; two square profiles generated by a vacuum pump operated for four seconds at 30 litres.minute^{-1} and 60 litres.minute^{-1}, and two profiles generated by the Hydraulic Lung, producing peak flow rates of approximately 45 and 60 litres.minute^{-1} (profiles 'D' and 'A' respectively). These are shown in Figure 5.4.

Figure 5.4 Test inhalation profiles



5.1.6. Test product and analysis

The study was conducted using Seretide Accuhaler, a commercially available dry powder inhaler delivering two drugs; salmeterol (50 micrograms per dose) and fluticasone propionate (100 micrograms per dose). The quantity of drug deposited on each stage of the MSLI was determined by HPLC analysis. Typically, four determinations were performed for each profile.

5.1.7. Results

The mean deposition profiles obtained for each drug across stages 2 to filter, approximately representing the 'respirable' particle sizes, expressed as a percentage of the total drug recovered are shown in Figures 5.5 and 5.6.

Figure 5.5 Deposition of Salmeterol in MSLI stages 2 to filter

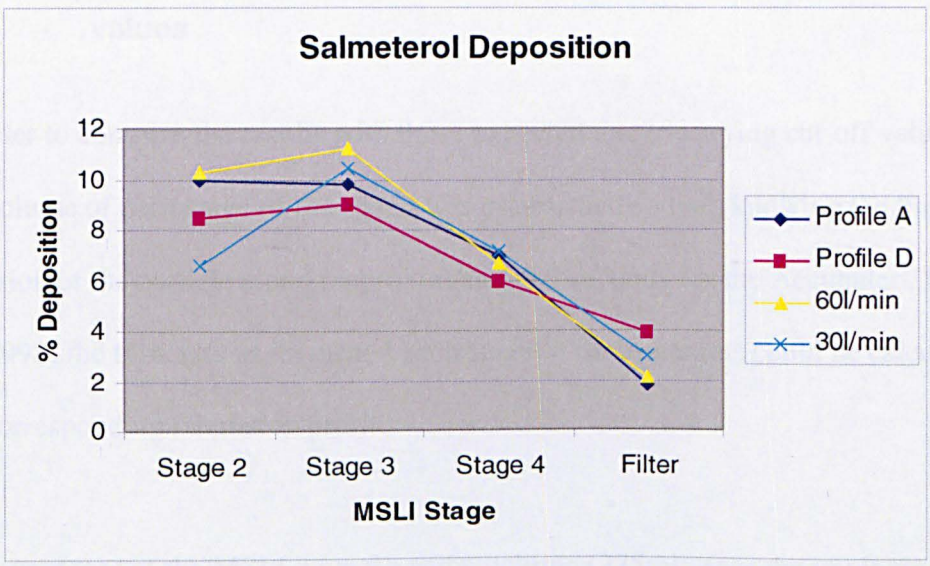
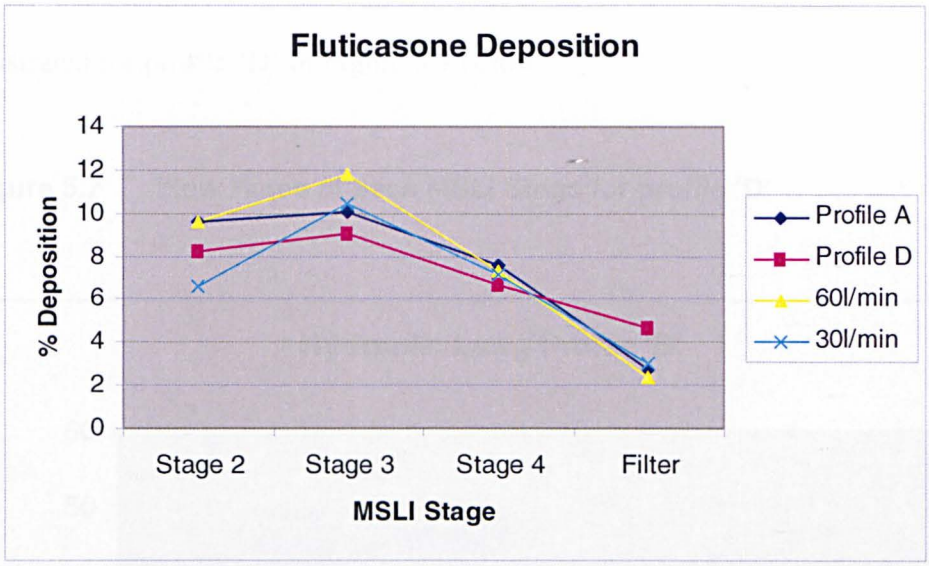


Figure 5.6 Deposition of Fluticasone Propionate in MSLI stages 2 to filter



It can be seen that the deposition patterns of the two drugs are very similar for a given flow profile. Each profile, however, produced a different deposition pattern.

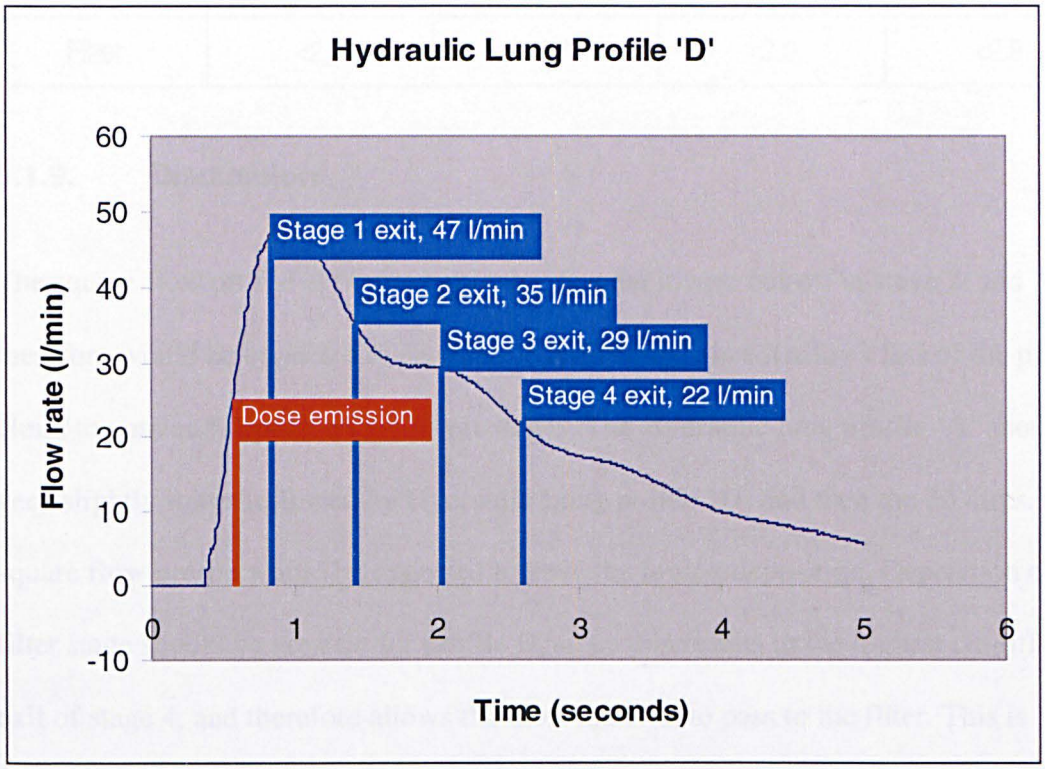
5.1.8. Establishing flow rates at each stage and consequent cut-off values

In order to compare the results with those expected due to varying cut-off values the volume of each stage of the MSLI was established so that, knowing the time of emission of the particle cloud (approximately 0.2 seconds for the Accuhaler , Burnell *et al.*, 1998) the flow rate as it reached each stage of the apparatus could be calculated from the corresponding inhalation profile.

All four stages of the MSLI have the same volume (275ml) once the impinging liquid is added. However, particles entering the apparatus also have to pass through the throat

which has a volume of 70ml. Once particles leave the DPI, therefore, they have to pass through 70 + 275 = 345ml volume before they encounter the cut-off at the exit of stage 1; a further 275ml before they encounter the cut-off at the exit of stage 2 and so on. This is illustrated for profile 'D' in Figure 5.7 below.

Figure 5.7 Flow Rates at each MSLI Stage for profile 'D'



It was assumed that the drug particles travel at approximately the same velocity as the air. The new cut-off values for each successive stage were calculated for each of the four profiles. The resultant size range of particles which should be collected on each stage is shown in Table 5.2.

Table 5.2 Calculated particle size ranges captured in the MSLI for each test profile

Stage of MSLI	Size Range 30 l/min (μm)	Size Range 60 l/min (μm)	Size Range HL (60 l/min) (μm)	Size Range HL (45 l/min) (μm)
Throat, Stages 1 &2	>9.6	>6.8	>7.0	>8.9
Stage 3	4.4-9.6	3.1-6.8	3.5-7.0	4.4-8.9
Stage 4	2.4-4.4	1.7-3.1	2.0-3.5	2.8-4.4
Filter	<2.4	<1.7	<2.0	<2.8

5.1.9. Discussion

The square flow profile at 60 litres.minute^{-1} has the lowest cut-off at stage 2, and therefore would be expected to capture the most drug, since it allows less of the particle cloud to pass and deposit on the lower stages. The Hydraulic lung profile 'A' should be very slightly lower followed by Hydraulic Lung profile 'D' and then the 30 litres.minute^{-1} square flow profile would be expected to have the lowest deposition. Deposition on the filter stage should be greatest for profile D, since this results in the highest cut-off at the exit of stage 4, and therefore allows the most material to pass to the filter. This is followed by the 30 litres.minute^{-1} profile, profile 'A' and then the 60 litres.minute^{-1} profile. It is difficult to predict the deposition patterns expected on stages 3 and 4 without a detailed knowledge of the particle size distribution of the emitted dose from the inhaler. However, the 30 litres.minute^{-1} profile and profile 'D' have the same calculated cut-off at the exit of stage 3, 4.4 microns, which allows a comparison to be made between these two. The 30 litres.minute^{-1} profile results in a wider size range being captured on stages 3 and 4 than profile 'D', and therefore more drug should be deposited. Comparisons

between predicted and observed patterns of deposition are presented in Table 5.3 and show excellent agreement. The apparatus (the combined Hydraulic Lung/ MSLI) appears to be working as expected and therefore should be capable of distinguishing between DPIs with different emission characteristics.

Table 5.3 Predicted and observed patterns of deposition in the MSLI

Stage	Predicted order of deposition	Observed order of deposition
Stage 2	60>A>D>30	60=A>D>30
Stage 3	30>D	30>D
Stage 4	30>D	30>D
Filter	D>30>A>60	D>30>A=60

5.1.10. Particle deposition within the lung

Particle deposition in the lungs can occur by a number of mechanisms in addition to impaction. Deposition may also occur by diffusion, sedimentation, interception and electrostatic attraction (Agnew, 1984).

Impaction depends on the size, density and velocity of particles, and occurs where the momentum of a particle is too great to allow it to undergo rapid changes in the direction of the airstream. Deposition by impaction is therefore more likely for larger, dense, fast moving particles.

Deposition by diffusion occurs when a particle is driven by the random collisions of gas molecules to land on the airway walls. Diffusion deposition becomes more significant as

particle size decreases, and is particularly important for particles of less than 1 micron diameter, especially in the lower airways where airway diameters are small and air velocities are low.

Deposition by sedimentation is due to the gravitational settling of particles. Like impaction, it is dependent on size, density and velocity, but occurs where the velocity is low.

Deposition by interception occurs where a particle is too large to pass through an airway. It is therefore dependent primarily on particle size and is most likely to take place in the lower airways.

Electrostatic deposition can occur where the inhaled particles carry a significant electrostatic charge which can induce an attractive 'image' charge on airway walls. Impaction and sedimentation are the most significant deposition mechanisms for particles delivered by inhalation (Agnew, 1984). Impaction is the dominant mechanism in the mouth, trachea, bronchi and larger bronchioles where there are many directional changes in the rapidly moving airstream, while the lower air velocities in the peripheral lung allow increased deposition by sedimentation.

5.1.11. Lung models for *in-vitro* testing of particle penetration

Other approaches to *in-vitro* determination of particle penetration, rather than particle sizing, have been taken using specialised apparatus. A model lung with the potential to

be used for this purpose was developed based on a series of three chambers, each containing glass beads. Each successive chamber contained beads of decreasing diameter so that the gaps between the beads, the 'airways', became increasingly small and associated with an increasingly large surface area for deposition by impaction, diffusion or gravitational settling. These dimensions were based on the Weibel lung model 'A' (Weibel, 1991) and resulted in linear air velocities in each stage which approximated those in the corresponding lung region (Ditchburn *et al.*, 1995 and unpublished thesis, 2000). However, testing was performed with a constant flow rate through the apparatus of 30 litres/minute rather than with a human-like inhalation. The predicted lung doses obtained with the apparatus for a Salbutamol MDI were in good agreement with values reported in *in-vivo* studies, in contrast to those from the Andersen Cascade Impactor.

A second *in-vitro* lung model, also developed at the University of Bath, was based on concentric shells (Hopkins, 1999 and 2001, PhD thesis, 2002). This concept originated with the mathematical transformation of lung geometry used to describe deposition in clinical studies using Single Proton Emission Computed Tomography (SPECT) techniques. Here, each lung was transformed into a series of ten, nested, hemispherical shells. The *in-vitro* model inspired by this used a single (right) lung comprising five shells for simplicity, made from aluminium and each with evenly spaced holes representing the airways. The holes in each successive shell decreased in diameter and increased in number such that, for example, shell 1 contained 7 x 5.4mm diameter holes and shell 4 contained 2500 x 0.99mm diameter holes. These dimensions, once again, were based on the Weibel 'A' model. A filter was used to capture all material not deposited inside shells 1 to 5. Tests performed on commercial inhaler products with this

model were, again, performed at constant flow rates, but demonstrated deposition by other mechanisms as well as impaction. Some degree of equivalence with in-vivo studies was also shown.

The MSLI used in this experiment has a volume of approximately 1.2 litres. This is significantly less than the volume of a typical human lung and is less than the volume of a typical inhalation (average inhalation in the current study was found to be 2.7 litres). It is possible, therefore, for particles which would penetrate only part-way into the lung before depositing by sedimentation to penetrate all through the MSLI apparatus. A more realistic test could be devised with further work using a slightly modified impinger apparatus providing a volume similar to that of the human lung by using appropriate spacers between each set of jets and impaction surface. This would allow the capture of particles by sedimentation at the appropriate 'depth' in the apparatus and further differentiation between devices. An appropriate settling period would have to be allowed before dismantling of the apparatus. Alternatively, the same approach could be taken with specifically designed model lungs, but the MSLI is readily available and could be modified quite cheaply. It would be interesting, though technically difficult, to simulate different emission characteristics by introducing aerosolised drug particles into the airstream at varying points in the inhalation. Ultimately, comparison of data with clinical evidence would be desirable to establish the validity of the approach.

5.2. *In-vitro* testing of DPIs with variable resistivity

5.2.1. Introduction

Current *in-vitro* testing of DPIs is based on performance of the device at a constant flow rate. The choice of flow rate may disregard the device resistance (eg. by using the 'traditional' flow rate of 60 litres.minute^{-1} for all devices) or it may be based on the flow rate achieved at a pressure drop across the device of 4 KPa as now recommended by the United States, European and British Pharmacopeias. (British Pharmacopoeia, 2002). In either case, device resistance is assumed to be constant, as a fluctuation in device resistance during the test would inevitably result in flow rate variation, since the pump is adjusted to provide the desired flow rate before the test 'inhalation' begins.

To date this assumption has been justifiable since all marketed DPIs have practically constant resistivity.

5.2.2. Designing DPIs with variable resistivity

The delivery of a drug by inhalation in a discrete bolus may provide improved targetting to a specific lung region. For example, it has been suggested that introducing the aerosol near the end of an inhalation at a high flow rate could be a means of effectively depositing drug on only the upper, conducting, airways (Bennett, 1991). Unfortunately, in a typical human inhalation profile the end of the inhalation is associated with a low flow rate, which would reduce the efficiency of this approach. A DPI with a resistivity which dropped significantly at the end of the inhalation could be used to provide the desired

flow profile for such an application. Similarly, a DPI which increased resistivity as flow increased could be used to moderate flow rates to decrease throat deposition or reduce flow related product variability. Many variations on these effects could be devised and achieved by a number of mechanical or electrical means.

The evolution of more sophisticated DPIs, therefore, may lead to variable resistance devices, since these may improve targeted delivery to the lungs or enhance aerosolisation of the powder formulation. The effect of variable device resistance on patient inhalation profiles has not been studied, but the Hydraulic Lung should be capable of predicting such effects since it can apply a given 'effort' to inhalation regardless of any changes in the device resistance.

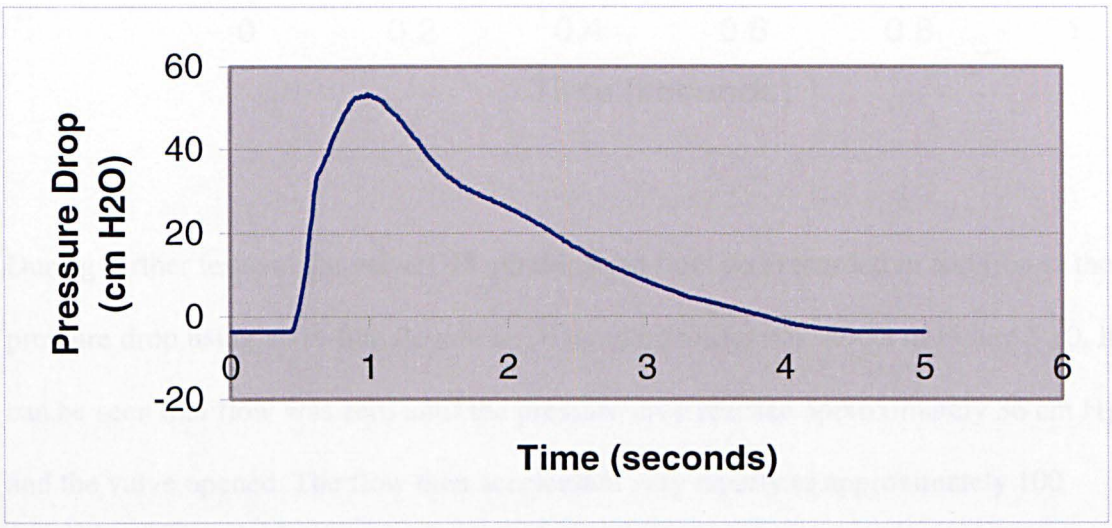
Preliminary tests using the Hydraulic Lung were performed on two model DPIs. The first was fitted with a one-way valve designed to open and allow the passage of air through the inhaler only when a required degree of effort was achieved i.e. the valve would have infinite resistance to airflow until it opened, at which point the resistance would drop rapidly to the inherent resistivity of the DPI itself. This was named the 'Valve DPI Model'. The second model was constructed with two flow paths, one of low and one of high resistivity. A 'flap' in a Venturi channel in the low resistivity flow path was designed to open when a pre-set pressure drop was achieved, diverting the flow through the high resistivity path and thereby limiting the achievable flow rate. This was named the 'Flow Limiting DPI Model'.

5.2.3. Results and Discussion

5.2.3.1. Testing on the Valve DPI Model

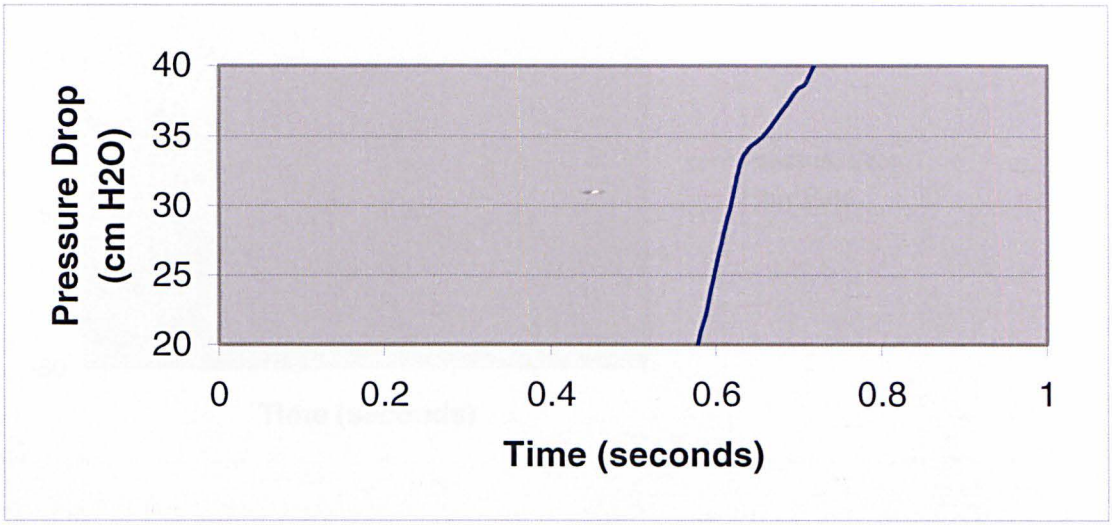
In the initial tests only pressure drop was recorded. A typical pressure drop profile during testing of the valve/DPI combination is shown in Figure 5.8.

Figure 5.8 Pressure drop profile with Valve DPI Model



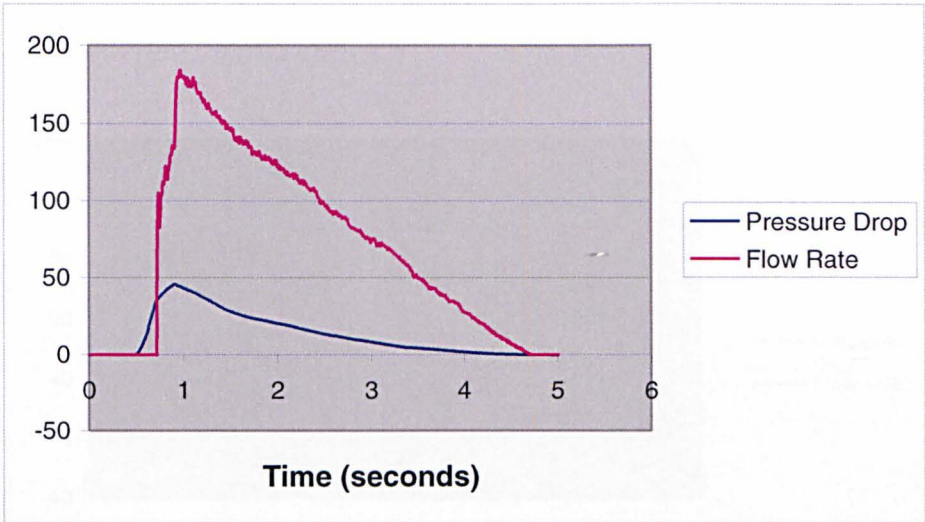
The point at which the valve opened is evident as a noticeable change in the rate of pressure increase at a pressure drop of approximately 34 cm H_2O, shown in the expanded profile in Figure 5.9

Figure 5.9 Change in rate of pressure drop increase as valve opened



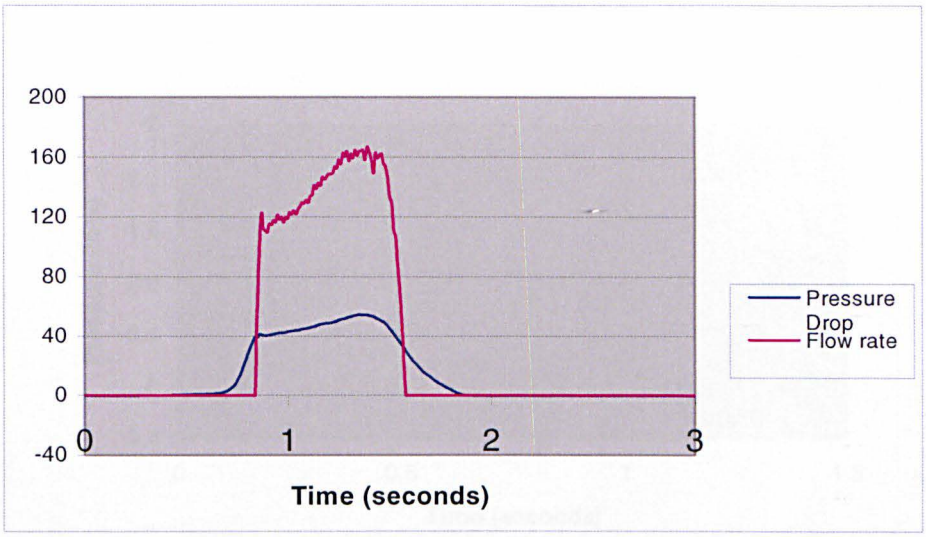
During further tests on the valve/DPI combination flow was recorded in addition to the pressure drop using an in-line flowmeter. Example profiles are shown in Figure 5.10. It can be seen that flow was zero until the pressure drop reached approximately 36 cm H_2O and the valve opened. The flow then accelerated very rapidly to approximately 100 litres.minute^{-1} and from that point onwards both pressure drop and flow rate profiles were typical for a system without a valve; both climbing to a maxima and then declining gradually until the inhalation was complete.

Figure 5.10 Flow and pressure drop profiles



Comparison with a human profile for inhalation through the valve (Figure 5.11) indicates the same characteristics i.e. rapid pressure increase until the valve opens followed by a lower rate of pressure increase until Pmax is attained. Flow is zero until the point at which the valve opens followed by a very rapid flow acceleration. The flow then climbs gradually to a maximum and declines to zero. These initial results suggest that the Hydraulic Lung behaves in the same manner as a typical human subject when inhaling through a simple variable resistance device, though further study and examination of more complex systems would be desirable.

Figure 5.11 Human flow and pressure drop profiles using the Valve DPI Model



5.2.3.2. Testing on the Flow Limiting DPI Model

Pressure drop profiles generated through the Flow Limiting DPI Model were collected using the Hydraulic Lung over a range of inspiratory efforts. It was found that the 'flap' activated at a pressure drop of approximately 2 kPa, switching flow from the low to high resistivity flow paths. In pressure drop profiles where 2 kPa was not achieved (for 20 and 22.5 cm columns of water, Figures 5.12 and 5.13) the flap did not activate and a smooth profile was observed .The activation of the flap was evident in some pressure drop profiles (25, 30 and 35cm columns of water, Figures 5.14, 5.15 and 5.16) where the sudden jump in resistivity resulted in a sharper rise in pressure drop.

Figure 5.12 Pressure drop profile with 20cm column of water

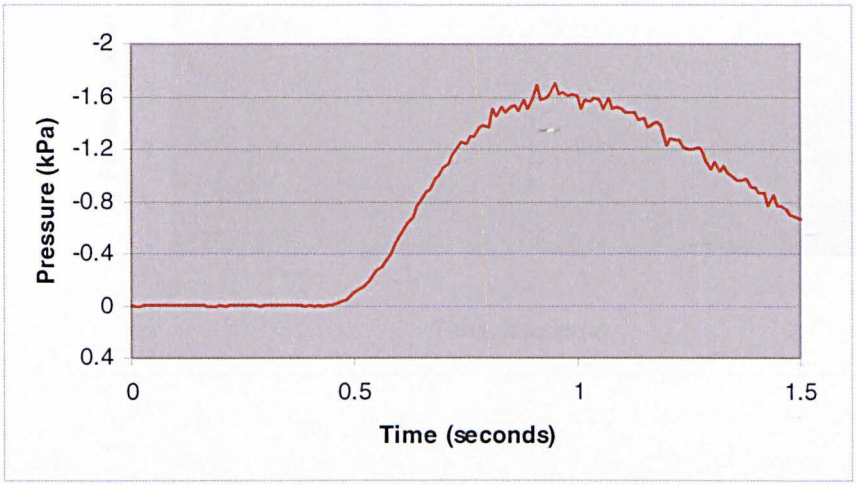


Figure 5.13 Pressure drop profile with 22.5cm column of water

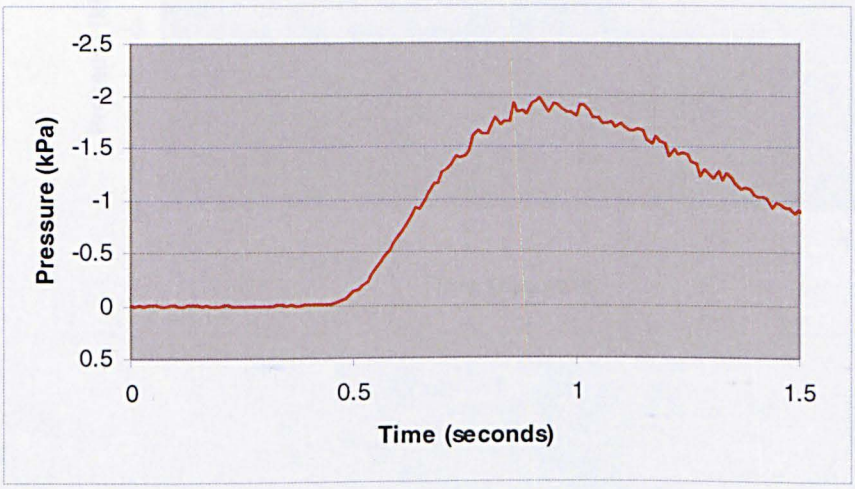


Figure 5.14 Pressure drop profile with 25cm column of water

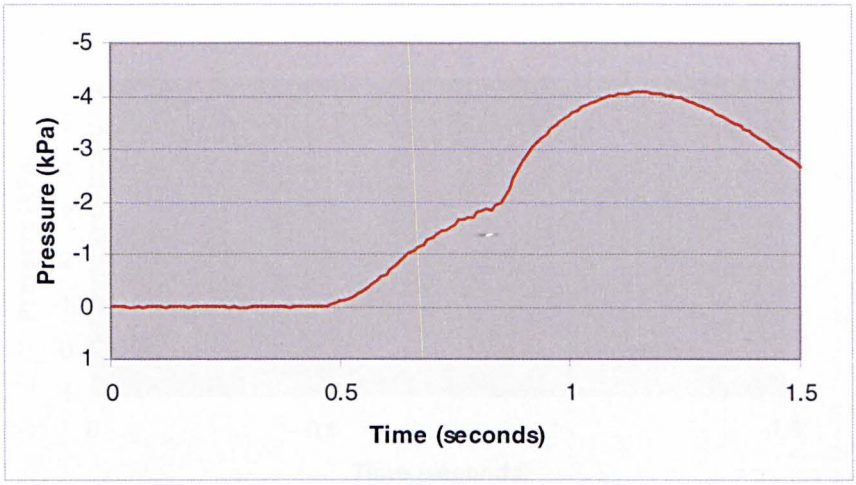


Figure 5.15 Pressure drop profile with 30cm column of water

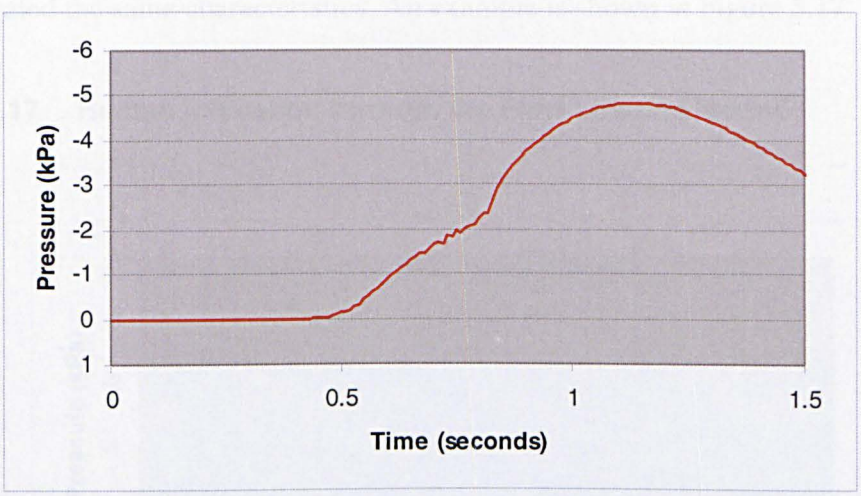
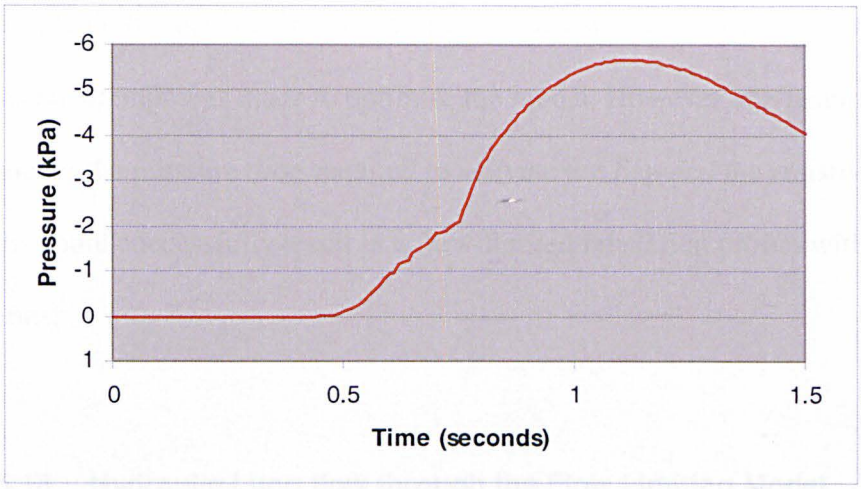
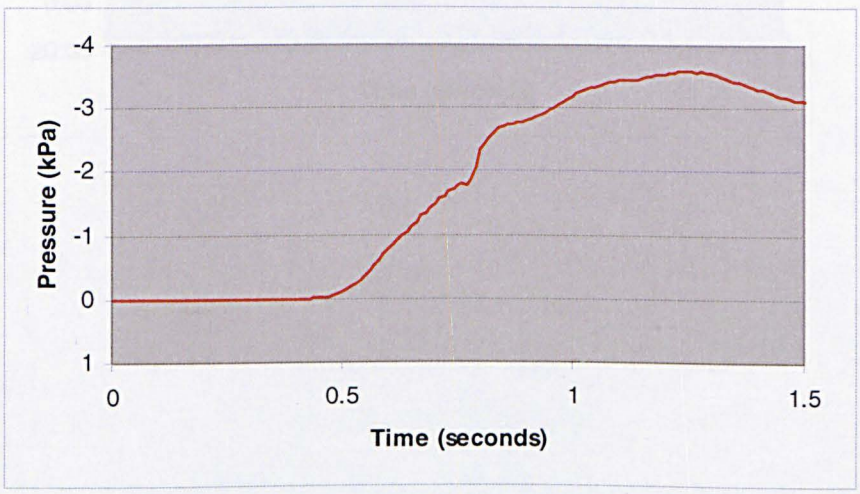


Figure 5.16 Pressure drop profile with 35cm column of water



Human inhalation profiles were also collected through the Flow Limiting Model and demonstrated the same characteristics. An example is shown in Figure 5.17.

Figure 5.17 Human inhalation through the Flow Limiting Model.



Displayed as flow rate profiles, Hydraulic Lung and Human inhalations are shown in Figures 5.18 and 5.19 respectively; suggesting that the Hydraulic Lung is capable of accurately predicting performance of the variable resistivity device in patient use. During these tests no attempt was made to optimise the model. However, the results also suggest that balancing the pressure drop required to activate the flap and the resistivity of the two flow paths could successfully result in a flow-limited inhalation profile with practical applications.

Figure 5.18 Hydraulic Lung flow through the Flow Limiting Model

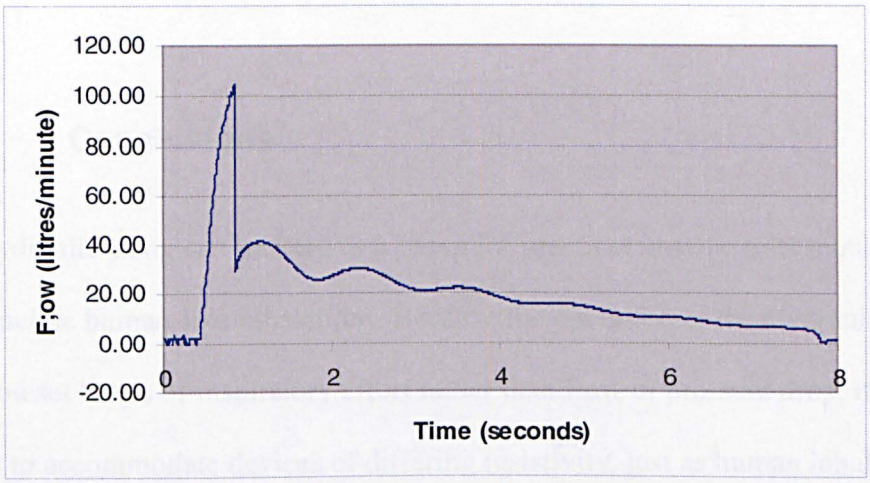
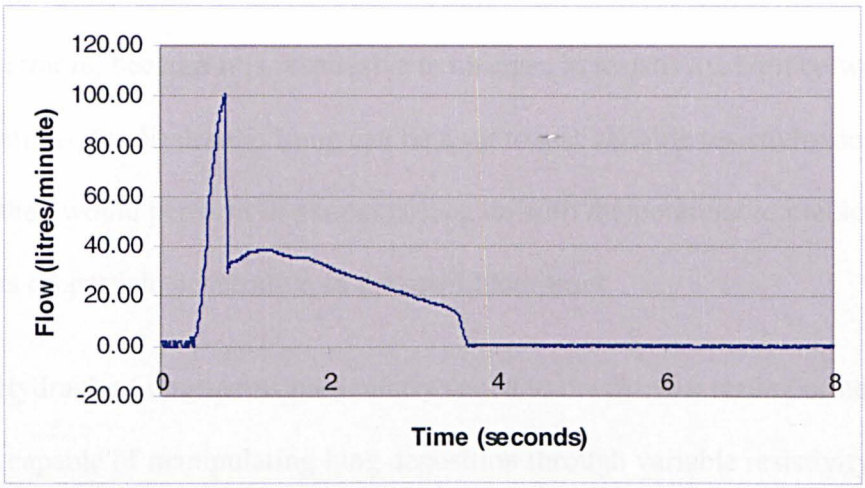


Figure 5.19 Human flow through the Flow Limiting Model



5.3. Conclusions

The Hydraulic Lung can be used as a pump for practical *in-vitro* tests requiring reproducible human-like inhalations. Because the operation of the Hydraulic Lung is based on set levels of inspiratory effort rather than flow or pressure drop, it will 'self-adjust' to accommodate devices of differing resistivity, just as human inhalation does. When designing new DPIs, attempts to increase turbulence and shear forces in order to enhance aerosolisation efficiency are likely to result in an increase in the resistivity of the device. The Hydraulic Lung could be used to explore the balance between increasing resistivity and increased flow rates where resistivity is low, to identify an optimum design for **Fine Particle Mass per unit effort.** It would be interesting to examine marketed inhalers with this in mind.

Using current or modified impinger/impactors, the Hydraulic Lung may be used to examine particle penetration including the effects of bolus delivery – a technique not possible with standard pump/impinger/impactor combinations.

Furthermore, because it is responsive to changes in resistivity, both between and within inhalations, the Hydraulic Lung can be used to test variable resistivity devices and predict how they would perform in patient use, again with the potential to predict resulting effects on particle penetration in the respiratory tract.

The Hydraulic Lung seems particularly suited to the *in-vitro* testing of next generation DPIs capable of manipulating lung deposition through variable resistivity and/or bolus delivery.

OVERVIEW, CONCLUSIONS AND FUTURE WORK

6.1. Overview

The characteristics of inhalation are dependent upon the equalisation of pressure within the lungs with the atmospheric pressure outside the lungs. The chest muscles which drive inhalation cannot expand the chest far against the force exerted by atmospheric pressure unless air is able to enter the lungs to reduce the pressure difference between the two. The rate at which air can pass into the lungs depends upon the magnitude of the pressure difference created by the chest muscles and the resistivity of the airways (or any device) between the lungs and the atmosphere. This in turn determines the rate at which further expansion of the chest can occur. In this thesis, a simple hydraulic apparatus has been used to model this process of inhalation, with the aim of mimicking human inhalation through resistant devices in order, primarily, to establish the relationship between inspiratory effort, resistivity and pressure drop. The value of this knowledge lies principally in its application to improved *in-vitro* testing of DPIs, where current standard tests are highly unrealistic, and comparisons between different types of devices are not generally conducted on a fair basis. The Hydraulic Lung has also been applied to some examples of practical in-vitro testing, where its ability to react to varying resistivity during an inhalation has particular advantages over standard apparatus.

Chapter 1 reviewed the reasons for the expansion of the DPI market and the growing variety of DPIs available and in development. The key *in-vitro* tests applied to DPIs were described, which historically employed a single flow rate for testing all devices. The evolution of this single flow rate approach into a variable flow rate system, based upon a single pressure drop, was discussed with its origin in a growing appreciation that:

a) patients achieve a wide range of flow rates which may vary markedly from one type of DPI to another.

b) test flow rate (and other inhalation characteristics) may have a significant effect on device performance.

This approach was, in part, based on the misconception that pressure drop could be equated to inspiratory effort across any device i.e. a patient would achieve the same pressure drop across any DPI.

The gap in current *in-vitro* testing of DPIs was therefore highlighted: a simple means to arrive at the appropriate test conditions for a given device of known resistivity and a fixed level of inspiratory effort appropriate to the desired patient group. Attempts to derive such a formula from clinical data were reviewed, and the potential advantage of working with a mechanical model, without the variability of human subjects, was proposed.

In Chapter 2 three designs for a mechanical model which could inhale like a human with a fixed level of inspiratory effort were considered. The original concept, a vertical syringe, was described and the flow/pressure drop profiles which would result from this design were deduced by consideration of the forces acting upon the system. The anticipated profile with a DPI of intermediate resistivity would differ from a typical human profile because having reached a flow or pressure drop maximum it would not then decline to zero. Although this problem could be overcome by modification of the design, the vertical syringe would be likely to suffer from some degree of irreproducibility due to frictional forces on the piston.

A second design, the 'bladder in a vacuum', was considered and the anticipated flow/pressure drop profiles found to be unlikely to reflect human inhalation, having maximum values at the very start of the inhalation. This design would also be likely to suffer from poor reproducibility over a period of time.

The third design discussed was based on a hydraulic system with a 'U'-tube concept. This design was considered to have significant advantages since it would be unlikely to suffer from variable friction effects and would provide a human-like inhalation profile which rose swiftly to a maximum value of flow or pressure drop and then declined gradually to zero. The Hydraulic Lung was therefore constructed and additional features such as a variable 'throat resistor' were included.

Materials used in the construction of the Hydraulic Lung were described in Chapter 3 together with descriptions of key equipment and methodology used in the research.

Chapter 4 described the experiment which generated the data set for the Hydraulic Lung and the clinical study which generated the equivalent human data set. Five resistors were chosen to represent a range of model DPIs. It was found that the twenty human volunteers, inhaling with maximal effort through the model DPIs, generated a very wide range of peak pressure drops, peak inspiratory flow rates (PIFRs), flow acceleration rates and inhaled volumes. This data set, generated for comparison with the Hydraulic Lung, is more comprehensive than those generated by either Clark and Hollingworth (1993) or Olsson and Asking (1994) as it includes both flow acceleration and inhaled volume measurements, and may therefore prove valuable for further research. The Hydraulic Lung was able to match approximately 60% of the observed range of human peak pressure drops, but would need to be redesigned or modified to achieve the full range.

The Hydraulic Lung, however, was found to be highly reproducible, and therefore more suitable for deriving an accurate relationship between key inhalation characteristics. Maximum Inspiratory Pressure (MIP) was defined as the measure of inspiratory effort, as this could be determined for both human subjects and the Hydraulic Lung.

A simple empirical formula for predicting pressure drop at any given level of resistivity and inspiratory effort was derived from the Hydraulic Lung data set. When this relationship was applied to the human data set, it was found that there was no significant difference between the predicted and observed values (at $P = 0.05$). The formula is easily adapted for predicting PIFR.

A second empirical equation relating flow acceleration, resistivity and inspiratory effort was derived but this was found to underestimate the flow acceleration values achieved by the human subjects. Modification of the apparatus would have to be considered to address this, though for practical purposes such as those discussed in Chapter 5 the flow acceleration values achieved by the Hydraulic Lung fell well within the range of the human data.

The results were compared to those reported in two key publications based on clinical studies. Differences between the results of this work and those of Clark and Hollingworth (1993) were discussed. Examination of the relationship found by Olsson and Asking (1994) between device resistance, PIFR and 'inspiratory force' revealed a correlation between 'inspiratory force' and inspiratory effort as defined by MIP, allowing their formula for PIFR to be adapted to use MIP values, and perhaps more easily related to different patient groups.

Practical applications of the Hydraulic Lung were explored in Chapter 5. Two main applications were considered; firstly, the use of the Hydraulic Lung to generate reproducible human-like inhalation profiles at a predetermined level of inspiratory effort in combination with a multi-stage impinger ; secondly as a resistivity-responsive pump to anticipate human inhalation through novel DPIs. In the first application a novel approach to the use of standard impingers was demonstrated, where particle penetration into the apparatus using a realistic inhalation profile was measured rather than particle size using a constant, 'square', flow rate profile. A comparison of deposition patterns resulting from square-wave and human-like profiles was found to correlate well with expected effects of varying flow on effective cut-off diameters. The Hydraulic Lung, being set to a specific inspiratory effort rather than a specific flow rate or pressure drop, could provide a comparative test of deposition efficiency between different devices in this way. Modification of standard apparatus such as the MSLI could enhance this approach. In the second application the utilisation of the Hydraulic Lung as a tool in device development was explored. Like a human, the Hydraulic Lung will react to sudden changes in device resistivity during an inhalation, and this was demonstrated for two test devices with variable resistivity, where Hydraulic Lung and human inhalations displayed the same characteristics.

6.2. Conclusions

- *In-vitro* testing of DPIs at a single flow rate or pressure drop does not provide a fair comparative test between devices with different resistivities. A change in device resistivity will generally result in a change in both peak flow rate and peak pressure drop for a given subject inhaling consistently.

- A simple mechanical device, the Hydraulic Lung, designed to inhale through DPIs with pre-determined levels of inspiratory effort was found to achieve the same peak pressure drop as a human when applying an equivalent level of inspiratory effort over a wide range of device resistivities.

- A simple equation was found to relate peak pressure drop, inspiratory effort and device resistivity. This equation may be used to predict the appropriate pressure drop for testing a DPI of given resistivity at a chosen level of inspiratory effort, thereby improving the practice of *in-vitro* testing. The equation may also be adapted to predict flow rate.

- The Hydraulic Lung, without modification, underestimates the flow acceleration achieved by humans when applying an equivalent level of inspiratory effort to a device of given resistivity. However, flow acceleration may be predicted using a simple relationship derived from the clinical data in this study.

- Humans vary greatly in their ability to apply inspiratory effort to inhalation through DPIs. As a result, key inhalation characteristics such as peak pressure drop, flow acceleration and inhaled volume which may affect both device performance and drug deposition in the lung also vary greatly. Within a group of twenty healthy volunteers a five-fold range for peak pressure drop and inhaled volume was typically observed for each model device, while that for flow acceleration could be greater than seventy-fold. This finding emphasises the need for the development of DPIs with minimal sensitivity to these variations.

- The Hydraulic Lung was found to be a useful practical tool for testing DPIs for either product comparisons or during product development. Since the Hydraulic Lung inhales with a pre-determined level of inspiratory effort it has advantages over standard test apparatus which operates on the basis of pre-determined pressure drop or flow rate, for example in the testing of DPIs with variable resistivity.

6.3. Future Work

6.3.1. Design modifications

Two shortcomings in the design of the current Hydraulic lung could be addressed by redesign:

- MIP values above 8 kPa cannot be achieved, though some healthy volunteers were able to produce MIPs of over 13 kPa.
- Flow acceleration rates in the Hydraulic Lung are lower than those typically observed for human subjects.

The MIP which can be generated within the Hydraulic Lung is dependent on a number of factors; principally the height of the liquid column above its rest position, the liquid density and the acceleration due to gravity. Since gravity is a constant for practical purposes, an increase in MIP would be most easily achieved by increasing the height of the water column. To achieve an MIP of 13 kPa would require the maximum height of the water column to increase by a factor of approximately 1.6, i.e. from 50cm to 80cm. The overall height of the current apparatus would have to be increased from 2.1 m to 2.4 m to accommodate this. An alternative approach could employ a higher density liquid

than water. It would not, however, be desirable to increase the viscosity of the liquid, as this might reduce the flow acceleration which can be achieved. An appropriate aqueous solution might be identified which would have a sufficiently high density without an increased viscosity. For example, a 4 molar solution of potassium bromide has a density of approximately 1.4 $g.cm^3$ and a viscosity of approximately 0.9 mPa.s (CRC Handbook, 2000). The increased density would allow the maximum MIP in the current apparatus to be increased to >11 kPa.

Fewer options are available to increase the flow acceleration within the Hydraulic Lung. Flow acceleration is determined by the rate at which the pressure drop within the apparatus is generated by the falling column of water (or other liquid). The rate of fall of the water is determined by the acceleration of gravity, which cannot be modified in a static apparatus. If the rate of fall of the water cannot be modified, the effect it has on the pressure within the apparatus can be modified to some extent, by altering the volume of the apparatus between the surface of the water and the resistance. The larger the volume of air within the apparatus the smaller the effect of an incremental drop in the water level on the pressure. Simplistically, if it were assumed that the rate of fall of the water level was not affected by the pressure in the apparatus at the start of the inhalation, i.e. while the pressure was very close to atmospheric pressure, and temperature effects were minimal, then Boyles' law would suggest:

$$P_1V_1 = P_2V_2$$

This means that halving the initial volume would double the effect on pressure drop when an incremental volume change occurred. Since flow is proportional to the square root of pressure drop, the 20% increase in flow acceleration required to match human inhalation might be achieved by a 45% reduction in the volume of the apparatus. This simplified approach would provide a starting point for such a modification. A reduction in headspace might also contribute to a higher MIP at a given height of water level, so some recalibration of this relationship would be necessary.

6.3.2. Effects of throat resistivity

The effects of varying throat resistivity have not been examined in this thesis. A single throat resistor, chosen to represent an average throat (section 4.4.1), has been used to generate the data discussed here. It would be interesting to study the effect of a throat resistor which fell within the range of device resistivities examined. It would be anticipated that if throat resistivity were significantly greater than device resistivity, the throat would dominate the resultant inhalation characteristics. Where device and throat resistivities were similar, both might have an influence. Differences in throat resistivities between patient or age groups reported in the literature could suggest appropriate experimental parameters.

6.3.3. Equilibration of 'lung' and 'throat' pressure drops

The introduction of a pressure tap into the apparatus between the water level and the throat resistor could be used to establish the existence of any delay between pressure changes in the 'lungs' and the 'throat' in the first phase of an inhalation as discussed in section 4.7.1.

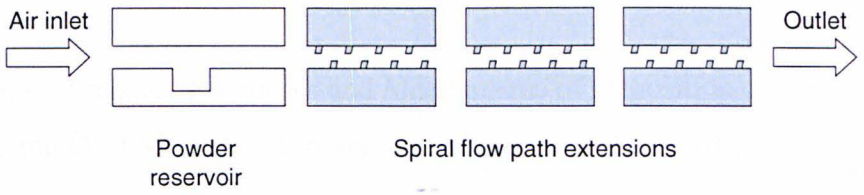
6.3.4. Studies on particle penetration

Modifications to the MSLI increasing the volume between impingement stages to provide a total volume closer to that of the human lung would be relatively simple to engineer, and would provide a useful tool for use with the Hydraulic Lung. The combined apparatus could be used to investigate the potential of variable resistivity devices to influence regional deposition of drug particles in the lungs. It could similarly be used to investigate the effects of bolus delivery of drug particles into pre-determined phases of the inhalation. In either case, the greatest benefit from such investigations would be gained by correlation with clinical data and determination of regional deposition in humans by such techniques as positron emission tomography (Rhodes and Hughes, 1995) or gamma-scintigraphy (Newman, 1993). Alternatively, other physical lung models such as those developed by Ditchburn *et al.* (1995) and Hopkins (1999) could be combined with the Hydraulic Lung in place of the MSLI.

6.3.5. Aerosolisation efficiency and inspiratory effort

The Hydraulic Lung could be used to compare the aerosolisation efficiency of commercially available DPIs at one or more levels of inspiratory effort. Alternatively, it could be used to optimise the design of a DPI for maximum efficiency at a given level of inspiratory effort. As an example, a simple test device could be constructed as shown in Figure 6.1.

Figure 6.1 Test device for aerosolisation efficiency



The test device would consist of a powder reservoir and a number of downstream flow path extensions which could be added to provide further turbulence purely by extension or perhaps by decreasing the diameter of the channel. Many variations on this theme could be tested. Additional turbulence in the airstream may increase particle deaggregation but it would also be likely to increase resistivity, resulting in a lower flow rate if tested at a constant level of inspiratory effort and potentially lower efficiency. The results of such a study would be interesting to correlate with a computational fluid dynamic evaluation of the system.

It was concluded that the Hydraulic Lung was able to accurately reproduce the key characteristics of human inhalation through DPIs and a simple relationship derived from the data could be used to calculate the appropriate test conditions for a given DPI and inspiratory effort,

It was concluded that the Hydraulic Lung was a useful practical tool in the development and testing of DPIs.

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APPENDIX A

Clinical Study Approval Application and Patient Information Document

Project No EC

EAST AND NORTH HERTFORDSHIRE HEALTH AUTHORITY

APPLICATION TO LOCAL RESEARCH ETHICS COMMITTEE

1. Title of project

Study to Compare Human and Hydraulic Lung Inhalation Characteristics.

2 Name and address of sponsor

GlaxoSmithKline Research and Development
Park Road
Ware
Herts
SG12 ODP

3. Name(s) and address(es) of local investigators

David Prime
Inhalation Product Development
GlaxoSmithKline Research and Development
Park Road
Ware
Herts
SG12 ODP

3. STUDY

3.1 What are the aims and objectives of the study?

This study will generate information on the inhalation characteristics of subjects inhaling through mock placebo Dry Powder Inhalers (DPIs). The information will be used to validate the use of a novel mechanical lung (the Hydraulic Lung) in the development and testing of improved DPIs for the treatment of asthma.

3.2 Have these aims and objectives been dealt with elsewhere? If so with what results?

No previous data have been generated to allow a direct comparison of the characteristics of human inhalation profiles with those generated by the Hydraulic Lung.

3.3 What is the study's background?

The Hydraulic Lung was developed to simulate human inhalation through DPIs in a realistic and highly reproducible manner. It will be used to establish the relationship between inhalation characteristics such as pressure drop, flow rate, flow acceleration or volume and device characteristics such as airflow resistance at varying levels of inspiratory effort. This information will allow the development of more realistic test methods for DPIs and hence improved design of future inhalation products.
The Hydraulic Lung project is a PhD research study. The human volunteer study is the second phase of the research programme. The data from human subjects will be compared to data which has already been generated on the Hydraulic Lung in order to establish if it is able to accurately simulate patient response to device characteristics.

3.4 What is the study's design?

A single-centre, single-blinded, two visit, 5-way crossover study randomised with respect to device order. At no time during the study will pharmacologically active drug substance be administered to the subjects.

On the first visit, subjects will be screened for compliance against inclusion/exclusion criteria. Subject demography will be recorded and then the subject will be trained to inhale on the model device with moderate resistance (orifice diameter 5mm) and test inhalation profiles (pressure drop versus time) will be recorded. Subjects will also be asked to inhale three times with maximal effort (i.e. as hard and fast as possible) using a model device of infinite resistance to establish their Maximum Inspiratory Pressure (MIP). This value indicates the level of inspiratory effort the subject can achieve.
Subjects covering a range of MIP values will be selected for the second visit.

On the second visit (7 days after the first visit) the subjects will be asked to perform a series of inhalations using five model devices of varying resistance, each time with maximal effort. The inhalation profiles will be recorded. Each device resistance will be tested in duplicate. The order of device resistances will be randomised. Subjects will be allowed to rest for 5 to 10 minutes between inhalations.

3.5 How are the results to be assessed?

After the first screening visit the MIP values for all subjects able to inhale through the devices in the prescribed manner will be reviewed. Subjects giving the highest and lowest values of inspiratory effort (MIP values) will be selected for the second visit in addition to a range of other subjects covering the intermediate values. A minimum of 12 and a maximum of 20 subjects will be chosen for the second visit.
The recorded pressure drop profiles will be transferred to a spreadsheet format and key inhalation characteristics such as peak pressure drop, peak flow rate etc derived from the data sets. The key inhalation characteristics will then be statistically evaluated for closeness of fit to the models derived from Hydraulic Lung data.

4. SUBJECTS

4.1 How many subjects are involved?

A minimum of 12 and a maximum of 20 subjects will be recruited into the study. This number is intended to allow a range of inspiratory efforts to be covered and to compensate for the variability of human inhalation profiles.

4.2 How are they selected?

Subjects will be healthy normal volunteers, males or females aged above 18 years, non-smokers, with no documented history of exercise induced asthma, an exacerbation of asthma or any respiratory condition. Subjects must be able to use the device satisfactorily, inhaling in the prescribed manner, after appropriate training.

4.3 Is there a control group?
(If yes, please give details)

No.

4.4 Are any groups excluded?
(If yes, please give details)

Subjects will be excluded if they fail to meet all of the inclusion criteria. Subjects will be excluded if they:

- Have a history of exercise induced asthma
- Have an exacerbation of asthma or any respiratory condition
- Cannot be trained to inhale through the test device in the prescribed manner

4.5 Are any payments made to subjects?
(If yes, please give details)

Subjects will be paid £10 per visit.

4.6 What will the subjects be told?
(Please enclose patient information form if one is available)

The background to the study will be explained to the subjects. Patient information is included in the consent form, a copy of which is appended.

4.7 Do the subjects give informed consent?
(Please enclose consent form if one is available)

Yes. A consent form is appended.

4.8 What are the criteria for patients being withdrawn from the study?

Subjects may withdraw at any time from the study for any reason. Also a subject could be withdrawn at any time by the investigator if it is judged detrimental for the subject to continue in the study. If a subject is withdrawn the reason for withdrawal will be recorded, along with information on any adverse event.

5. ADMINISTRATION

5.1 What drugs will be administered?

No drugs will be administered at any time.

5.2 Is a clinical trial certificate required?
(If yes, please give details)

No.

5.3 What samples are to be taken?

No samples are to be taken.

5.4 What tests are to be undertaken?

No tests are to be undertaken.

5.5 What procedures are to be undertaken?

On the first visit, subjects will be trained to inhale on the model device with moderate resistance (orifice diameter 5mm) and test inhalation profiles will be recorded. Subjects will also be asked to inhale three times with maximal effort (i.e. as hard and fast as possible) using a model device of infinite resistance to establish their Maximum Inspiratory Pressure (MIP). This value indicates the level of inspiratory effort the subject can achieve. Subjects covering a range of MIP values will be selected for the second visit.

On the second visit (7 days after the first visit) the subjects will be asked to perform a series of inhalations using five model devices of varying resistance, each time with maximal effort. The inhalation profiles will be recorded. Each device resistance will be tested in duplicate. The order of device resistances will be randomised. Subjects will be allowed to rest for 5 to 10 minutes between inhalations.

5.6 What discomfort may occur in some or all of the subjects?

Subjects may experience minor discomfort such as drying of the throat and mouth as they inhale ambient air but this may be alleviated by drinking water between inhalations if desired.

5.7 Are there any possible dangers?
(If yes, please give details)

A risk assessment has been performed and is included in the appended Technical Memorandum.

5.8 Is a questionnaire to be used?
(If yes, please enclose a copy)

No.

6. IMPLICATIONS FOR THE NHS

6.1 Are there any financial implications for the NHS?
(If yes, please give details)

No.

6.2 Are there any workload implications for the NHS?
(If yes, please give details)

No.

6.3 Have any implications been discussed with the NHS departments concerned?
(Please give details)

Not applicable.

6.4 What indemnity arrangements have been made?

The standard GSK indemnity arrangements will be followed; the agreement is appended to this form.

6.5 What payments will be made to the investigators?

None.

7. APPROVALS

7.1 Is approval of the subject's GP being obtained?
(Please give details)

No.

7.2 Is this a multi-centre study?
(If yes, please give details)

No.

7.3 Is approval being sought from other ethical committees?
(If yes, please give details)

No.

Signature : .....

Name printed : .....

Address :.....

.....

Date form completed : .....

Please send completed form to Jean Hussein, Secretary to the East and North Hertfordshire LREC, Directorate of Public Health, Charter House, Parkway, Welwyn Garden City, AL8 6JL

For studies submitted by nursing students at the University of Hertfordshire:
To be completed by the study supervisor

I support the application as set out in the application form:

Signature :.....

Name printed :.....

Title :.....

Inhalation Profile Recording of Volunteers at Ware

Patient Information and Consent Document

You are being invited to take part in a research study. This information sheet explains why the research is being done and what it will involve. Please take time to read the following information carefully and if anything is not clear, or if you would like further information, please ask.

Thank you for reading this.

What is the purpose of this study?

Dry Powder Inhalers (DPIs) such as the Diskus device developed and marketed by GlaxoSmithKline now form an important part of the range of therapies available for the treatment of asthma and chronic obstructive pulmonary disease. There are many such inhalers available from different pharmaceutical companies and they vary in their suitability for use by different patient groups. For example, an inhaler which takes quite a lot of effort to inhale (breath in) through, might be unsuitable for young children or the very sick to use because they can only pull a very low flow rate through the inhaler.

Laboratory testing of these inhalers is often used to compare different types of DPIs against one another to show how well, and how consistently they deliver doses of drug. These comparisons are quite useful but they can also be unrealistic. For example, it is quite usual to compare inhalers by testing them all at the same flowrate. This is not realistic, because given two different types of inhaler it is very unlikely that a single patient would achieve the same flow rate through both of them. It is as if inhalers were being compared by giving one to a healthy person to inhale through and another to a severe asthmatic. As the flow rate can have an important effect on the performance of some inhalers, we need to understand how flow rates

are affected by the design of the inhaler and how hard a patient can inhale. Then we can compare inhalers fairly, as if they were all being used by the same patient.

An apparatus called the Hydraulic Lung has been developed which can inhale through DPIs in the same way as people do; and it can be adjusted to inhale like a child or an adult, a healthy person or one who suffers from asthma. The Hydraulic Lung can be used to study how people inhale through different kinds of inhaler, and how we can improve laboratory testing to make it more realistic. To prove that it works correctly, however, we need to compare the information it gives to information from volunteers. To do this, we need volunteers to inhale through a range of empty model inhalers, which contain no drug, so that air flow rates can be measured.

Who will take part in this study?

Volunteers for this study will be recruited from within the staff at GlaxoSmithKline, Ware; the study being advertised by e-mail.

Approximately twenty volunteers will be involved. All will be over eighteen years of age, non-smokers with no history of exercise induced asthma and no exacerbation of asthma or any other respiratory condition.

It is up to you to decide whether or not you wish to take part. If you decide to take part you will be given a copy of this information sheet to keep and be asked to sign to indicate your consent. If you decide to take part you are still free to withdraw at any time without giving a reason.

What will happen to me if I take part?

If you decide to take part you will be asked to make either one or two visits to the Occupational Health Centre at Ware.

On the first visit you will be asked for information to indicate that you are suitable to take part in the study (e.g. you are a non-smoker), and to give some facts about yourself.

You will then be asked to practise breathing in through a model inhaler and, thereafter, to make three inhalations through the device with maximal effort (i.e. as hard and fast as you can) so that air flows can be recorded.

You may be asked to make a second visit, one week later. At the second visit you will be asked to make two inhalations through each of five model devices, each at maximal effort. You will be allowed to rest for five to ten minutes between inhalations if you wish.

Each visit could take up to one hour. You will be paid £10 for each visit to compensate for any inconvenience.

Are there any risks or benefits in taking part?

All of the model devices are empty and contain no drugs. Inhaling air through the model devices as if they were real inhalers will allow us to measure air flow rates.

There is no clinical benefit in taking part in the study and the information generated is for research purposes only; data from the study will form part of a PhD research project. All information which is collected about you during the study will remain confidential.

Who has sponsored and reviewed the study?

The study is sponsored by GlaxoSmithKline Research and Development and has been reviewed and approved by the East and North Hertfordshire Local Research Ethics Committee.

Who can provide further information?

For any further information you can contact David Prime, Inhalation Product Development, at Ware.

I have read the above Volunteer information and agree to take part in the study.

Signed..... Date.....

Please print name.....

20/4/01 Version 2.

APPENDIX B

Hydraulic Lung Data

APPENDIX B **Hydraulic Lung Data**

resistor	resistor diameter (mm)	resistivity ($kPa^{0.5}$.$litres^{-1}$.minute)	effort (cm water)	Maximum Inspiratory Pressure (kPa)	pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}$.$second^{-1}$)	volume (litres)
A	3	0.0478	15	3.51	2.60	34.38	68.76	1.08
A	3	0.0478	15	3.51	2.60	34.38	68.30	1.08
A	3	0.0478	20	4.90	3.75	41.50	89.57	1.44
A	3	0.0478	20	4.90	3.76	41.50	90.34	1.44
A	3	0.0478	25	6.03	4.71	46.56	109.92	1.77
A	3	0.0478	25	6.03	4.69	46.56	103.05	1.76
A	3	0.0478	30	6.85	5.44	49.94	118.74	2.11
A	3	0.0478	30	6.85	5.44	49.94	121.92	2.10
A	3	0.0478	35	7.65	6.09	53.05	137.61	2.41
A	3	0.0478	35	7.65	6.11	53.05	134.81	2.41
A	3	0.0478	40	8.31	6.81	55.49	144.20	2.73
A	3	0.0478	40	8.31	6.77	55.49	156.40	2.74
A	3	0.0478	45	9.10	7.41	58.29	163.36	3.06
A	3	0.0478	45	9.10	7.37	58.29	155.24	3.05
A	3	0.0478	50	9.73	7.95	60.44	182.11	3.36
A	3	0.0478	50	9.73	7.97	60.44	176.13	3.37

APPENDIX B **Hydraulic Lung Data** **(continued)**

resistor	resistor diameter (mm)	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	effort (cm water)	Maximum Inspiratory Pressure (kPa)	pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
B	4.5	0.0323	15	3.51	2.12	47.46	95.03	1.05
B	4.5	0.0323	15	3.51	2.15	47.46	94.40	1.03
B	4.5	0.0323	20	4.90	3.16	57.99	124.56	1.36
B	4.5	0.0323	20	4.90	3.15	57.99	122.08	1.36
B	4.5	0.0323	25	6.03	4.04	65.48	150.09	1.69
B	4.5	0.0323	25	6.03	4.05	65.48	149.06	1.69
B	4.5	0.0323	30	6.85	4.74	70.49	175.11	2.02
B	4.5	0.0323	30	6.85	4.76	70.49	182.76	2.02
B	4.5	0.0323	35	7.65	5.36	75.09	194.12	2.31
B	4.5	0.0323	35	7.65	5.36	75.09	195.96	2.33
B	4.5	0.0323	40	8.31	5.97	78.70	216.63	2.64
B	4.5	0.0323	40	8.31	5.96	78.70	212.19	2.64
B	4.5	0.0323	45	9.10	6.54	82.85	231.26	2.96
B	4.5	0.0323	45	9.10	6.56	82.85	225.71	2.96
B	4.5	0.0323	50	9.73	7.11	86.03	239.54	3.26
B	4.5	0.0323	50	9.73	7.08	86.03	257.51	3.28

APPENDIX B **Hydraulic Lung Data** **(continued)**

resistor	resistor diameter (mm)	resistivity ($kPa^{0.5}$.$litres^{-1}$ .minute)	effort (cm water)	Maximum Inspiratory Pressure (kPa)	pressure drop (kPa)	Peak Inspiratory Flow Rate (litres.$minute^{-1}$)	flow acceleration (litres.$minute^{-1}$.$second^{-1}$)	volume (litres)
C	5	0.0264	15	3.51	2.00	55.18	118.36	1.15
C	5	0.0264	15	3.51	2.03	55.18	115.55	1.16
C	5	0.0264	20	4.90	3.10	68.07	149.38	1.54
C	5	0.0264	20	4.90	3.15	68.07	151.35	1.67
C	5	0.0264	25	6.03	3.95	77.23	186.58	1.90
C	5	0.0264	25	6.03	3.95	77.23	190.01	1.89
C	5	0.0264	30	6.85	4.65	83.36	209.81	2.26
C	5	0.0264	30	6.85	4.62	83.36	208.02	2.28
C	5	0.0264	35	7.65	5.27	88.98	234.09	2.63
C	5	0.0264	35	7.65	5.24	88.98	240.00	2.63
C	5	0.0264	40	8.31	5.89	93.41	262.49	3.01
C	5	0.0264	40	8.31	5.87	93.41	254.25	3.01
C	5	0.0264	45	9.10	6.45	98.48	285.19	3.38
C	5	0.0264	45	9.10	6.43	98.48	289.47	3.38
C	5	0.0264	50	9.73	6.90	102.37	309.57	3.74
C	5	0.0264	50	9.73	6.90	102.37	303.79	3.72

APPENDIX B **Hydraulic Lung Data** **(continued)**

resistor	resistor diameter (mm)	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	effort (cm water)	Maximum Inspiratory Pressure (kPa)	pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
D	6	0.0171	15	3.51	1.49	71.94	169.29	1.30
D	6	0.0171	15	3.51	1.49	71.94	171.00	1.29
D	6	0.0171	20	4.90	2.39	91.83	223.29	1.70
D	6	0.0171	20	4.90	2.48	91.83	215.95	1.71
D	6	0.0171	25	6.03	3.27	105.98	259.48	2.13
D	6	0.0171	25	6.03	3.27	105.98	237.73	2.12
D	6	0.0171	30	6.85	3.88	115.44	302.40	2.54
D	6	0.0171	30	6.85	3.87	115.44	300.36	2.53
D	6	0.0171	35	7.65	4.45	124.13	343.92	2.93
D	6	0.0171	35	7.65	4.45	124.13	340.61	2.93
D	6	0.0171	40	8.31	5.05	130.96	365.00	3.34
D	6	0.0171	40	8.31	4.98	130.96	396.57	3.33
D	6	0.0171	45	9.10	5.49	138.79	465.63	3.73
D	6	0.0171	45	9.10	5.48	138.79	464.45	3.74
D	6	0.0171	50	9.73	5.93	144.80	538.53	4.11
D	6	0.0171	50	9.73	5.92	144.80	541.75	4.12

APPENDIX B **Hydraulic Lung Data (continued)**

resistor	resistor diameter (mm)	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	effort (cm water)	Maximum Inspiratory Pressure (kPa)	pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
E	7	0.0138	15	3.51	1.13	78.00	256.39	1.31
E	7	0.0138	15	3.51	1.11	78.00	233.00	1.31
E	7	0.0138	20	4.90	1.91	102.64	239.13	1.71
E	7	0.0138	20	4.90	1.94	102.64	259.13	1.72
E	7	0.0138	25	6.03	2.85	120.18	302.68	2.21
E	7	0.0138	25	6.03	2.81	120.18	289.69	2.20
E	7	0.0138	30	6.85	3.37	131.89	336.10	2.62
E	7	0.0138	30	6.85	3.38	131.89	332.79	2.63
E	7	0.0138	35	7.65	3.90	142.66	414.26	3.02
E	7	0.0138	35	7.65	3.92	142.66	420.72	3.03
E	7	0.0138	40	8.31	4.31	151.13	496.26	3.42
E	7	0.0138	40	8.31	4.30	151.13	472.55	3.43
E	7	0.0138	45	9.10	4.70	160.83	500.57	3.82
E	7	0.0138	45	9.10	4.75	160.83	472.31	3.84
E	7	0.0138	50	9.73	5.10	168.27	564.44	4.21
E	7	0.0138	50	9.73	5.13	168.27	553.74	4.20

APPENDIX C

Clinical Study Data

APPENDIX C Clinical Study Data

subject	resistor	resistivity ($kPa^{0.5}litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
1	A	0.0478	6.62	6.25	4.71	45.42	89.62	1.52
1	A	0.0478	6.62	6.25	5.16	47.52	79.91	1.46
1	B	0.0323	6.62	6.25	5.22	70.73	115.26	1.70
1	B	0.0323	6.62	6.25	5.24	70.87	103.44	1.72
1	C	0.0264	6.62	6.25	4.39	79.33	218.10	1.34
1	C	0.0264	6.62	6.25	4.98	84.50	250.99	1.66
1	D	0.0171	6.62	6.25	2.93	97.18	88.52	1.81
1	D	0.0171	6.62	6.25	2.98	98.06	196.70	1.80
1	E	0.0138	6.62	6.25	3.13	118.75	310.20	1.89
1	E	0.0138	6.62	6.25	3.13	118.77	249.01	1.80
2	A	0.0478	5.05	9.08	6.24	52.28	97.59	1.61
2	A	0.0478	5.05	9.08	8.53	61.11	148.26	0.76
2	B	0.0323	5.05	9.08	5.85	74.90	196.39	2.01
2	B	0.0323	5.05	9.08	6.42	78.46	182.10	2.50
2	C	0.0264	5.05	9.08	5.27	86.98	263.10	2.39
2	C	0.0264	5.05	9.08	6.02	92.94	231.22	2.07
2	D	0.0171	5.05	9.08	1.96	79.47	441.72	2.42
2	D	0.0171	5.05	9.08	3.84	111.31	162.48	3.12
2	E	0.0138	5.05	9.08	4.24	138.22	354.64	3.17
2	E	0.0138	5.05	9.08	4.57	143.43	258.72	3.33

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}$.$litres^{-1}$ .minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate (litres.$minute^{-1}$)	flow acceleration (litres.$minute^{-1}$.$second^{-1}$)	volume (litres)
3	A	0.0478	12.88	9.98	8.54	61.12	187.27	2.44
3	A	0.0478	12.88	9.98	7.80	58.41	294.58	3.87
3	B	0.0323	12.88	9.98	6.58	79.42	358.52	4.52
3	B	0.0323	12.88	9.98	7.48	84.68	340.57	4.72
3	C	0.0264	12.88	9.98	7.39	102.98	487.78	4.35
3	C	0.0264	12.88	9.98	6.05	93.15	544.80	4.75
3	D	0.0171	12.88	9.98	5.28	130.55	443.90	4.55
3	D	0.0171	12.88	9.98	6.25	142.06	536.09	5.18
3	E	0.0138	12.88	9.98	4.85	147.80	592.61	4.57
3	E	0.0138	12.88	9.98	4.12	136.21	549.47	4.73
4	A	0.0478	11.89	10.94	8.53	61.11	297.36	0.76
4	A	0.0478	11.89	10.94	9.46	64.35	240.17	0.86
4	B	0.0323	11.89	10.94	8.12	88.21	409.57	1.25
4	B	0.0323	11.89	10.94	7.95	87.32	507.11	1.44
4	C	0.0264	11.89	10.94	7.03	100.41	681.50	1.57
4	C	0.0264	11.89	10.94	7.32	102.46	653.71	1.33
4	D	0.0171	11.89	10.94	6.70	147.12	1116.92	2.19
4	D	0.0171	11.89	10.94	7.10	151.40	762.88	2.01
4	E	0.0138	11.89	10.94	5.21	153.24	1275.52	2.12
4	E	0.0138	11.89	10.94	5.78	161.38	1384.64	2.32

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
5	A	0.0478	14.09	14.88	12.16	72.95	350.25	3.09
5	A	0.0478	14.09	14.88	12.67	74.47	249.51	2.97
5	B	0.0323	14.09	14.88	11.15	103.38	426.03	3.18
5	B	0.0323	14.09	14.88	10.26	99.16	443.12	3.17
5	C	0.0264	14.09	14.88	9.45	116.43	533.37	3.39
5	C	0.0264	14.09	14.88	9.25	115.22	677.16	3.63
5	D	0.0171	14.09	14.88	7.36	154.17	905.52	3.06
5	D	0.0171	14.09	14.88	7.32	153.70	835.81	3.96
5	E	0.0138	14.09	14.88	8.23	192.56	1280.68	4.27
5	E	0.0138	14.09	14.88	7.69	186.06	954.10	4.04
6	A	0.0478	4.51	3.73	2.51	33.12	148.56	0.70
6	A	0.0478	4.51	3.73	2.99	36.20	57.83	0.86
6	B	0.0323	4.51	3.73	2.14	45.28	216.74	1.05
6	B	0.0323	4.51	3.73	1.79	41.40	154.30	0.78
6	C	0.0264	4.51	3.73	2.30	57.44	239.00	1.25
6	C	0.0264	4.51	3.73	2.88	64.27	185.57	1.17
6	D	0.0171	4.51	3.73	1.56	70.86	497.20	1.42
6	D	0.0171	4.51	3.73	2.64	92.40	303.05	1.30
6	E	0.0138	4.51	3.73	1.05	68.61	313.75	1.88
6	E	0.0138	4.51	3.73	1.71	87.81	313.01	1.96

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
7	A	0.0478	12.29	10.93	8.47	60.89	84.64	2.85
7	A	0.0478	12.29	10.93	9.50	64.48	162.89	3.33
7	B	0.0323	12.29	10.93	7.53	84.96	241.92	3.33
7	B	0.0323	12.29	10.93	8.15	88.38	197.98	3.70
7	C	0.0264	12.29	10.93	5.53	89.08	2029.26	4.86
7	C	0.0264	12.29	10.93	8.14	108.07	383.45	3.67
7	D	0.0171	12.29	10.93	6.89	149.15	496.02	4.58
7	D	0.0171	12.29	10.93	6.47	144.55	507.44	4.78
7	E	0.0138	12.29	10.93	4.60	143.98	1265.77	4.29
7	E	0.0138	12.29	10.93	5.16	152.39	2500.77	4.88
8	A	0.0478	13.52	10.24	7.40	56.91	54.84	1.50
8	A	0.0478	13.52	10.24	9.38	64.09	160.71	1.68
8	B	0.0323	13.52	10.24	4.81	67.91	96.84	1.35
8	B	0.0323	13.52	10.24	8.24	88.84	167.27	1.91
8	C	0.0264	13.52	10.24	7.38	102.91	157.10	2.09
8	C	0.0264	13.52	10.24	6.62	97.43	146.81	1.82
8	D	0.0171	13.52	10.24	4.45	119.87	548.23	2.18
8	D	0.0171	13.52	10.24	4.91	125.84	297.62	2.19
8	E	0.0138	13.52	10.24	2.55	107.26	321.51	1.49
8	E	0.0138	13.52	10.24	4.82	147.42	139.30	2.20

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}$.$litres^{-1}$ .minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate (litres.$minute^{-1}$)	flow acceleration (litres.$minute^{-1}$.$second^{-1}$)	volume (litres)
9	A	0.0478	4.96	10.49	8.59	61.31	372.92	0.77
9	A	0.0478	4.96	10.49	8.62	61.44	386.74	0.69
9	B	0.0323	4.96	10.49	8.32	89.32	553.54	0.88
9	B	0.0323	4.96	10.49	8.62	90.90	557.63	0.99
9	C	0.0264	4.96	10.49	6.29	94.98	219.15	1.44
9	C	0.0264	4.96	10.49	6.61	97.42	502.37	1.24
9	D	0.0171	4.96	10.49	6.92	149.51	971.81	1.62
9	D	0.0171	4.96	10.49	6.97	150.01	919.99	1.62
9	E	0.0138	4.96	10.49	4.93	149.00	1027.67	1.72
9	E	0.0138	4.96	10.49	6.52	171.34	1162.72	1.94
10	A	0.0478	11.39	12.47	10.42	67.54	250.46	2.07
10	A	0.0478	11.39	12.47	10.23	66.92	211.89	2.38
10	B	0.0323	11.39	12.47	10.57	100.63	371.41	2.72
10	B	0.0323	11.39	12.47	9.73	96.59	378.20	2.65
10	C	0.0264	11.39	12.47	9.36	115.88	532.87	2.86
10	C	0.0264	11.39	12.47	9.39	116.07	508.31	2.90
10	D	0.0171	11.39	12.47	8.79	168.46	854.68	3.72
10	D	0.0171	11.39	12.47	9.18	172.15	1085.75	4.21
10	E	0.0138	11.39	12.47	8.49	195.51	873.10	4.03
10	E	0.0138	11.39	12.47	7.74	186.72	730.97	3.93

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
11	A	0.0478	10.28	10.87	8.59	61.32	304.06	1.38
11	A	0.0478	10.28	10.87	9.28	63.74	284.29	1.46
11	B	0.0323	10.28	10.87	8.55	90.52	389.84	1.64
11	B	0.0323	10.28	10.87	8.23	88.84	416.61	1.56
11	C	0.0264	10.28	10.87	8.28	129.04	709.71	2.63
11	C	0.0264	10.28	10.87	8.07	127.36	777.22	2.96
11	D	0.0171	10.28	10.87	6.25	142.00	733.57	2.81
11	D	0.0171	10.28	10.87	6.60	145.92	367.88	2.81
11	E	0.0138	10.28	10.87	5.07	151.13	976.17	3.10
11	E	0.0138	10.28	10.87	5.92	163.25	762.90	2.97
12	A	0.0478	8.04	10.72	9.16	63.30	265.74	1.26
12	A	0.0478	8.04	10.72	8.46	60.83	200.44	1.28
12	B	0.0323	8.04	10.72	8.29	89.16	303.89	2.03
12	C	0.0264	8.04	10.72	7.45	122.39	724.35	2.97
12	C	0.0264	8.04	10.72	7.72	124.61	759.54	2.52
12	D	0.0171	8.04	10.72	5.36	131.52	874.24	2.87
12	D	0.0171	8.04	10.72	5.81	136.92	711.43	2.98
12	E	0.0138	8.04	10.72	5.96	163.84	758.13	3.42
12	E	0.0138	8.04	10.72	6.27	168.03	576.13	3.00

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}$.$litres^{-1}$ .minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}$.$second^{-1}$)	volume (litres)
13	A	0.0478	12.30	13.52	11.47	70.86	269.03	3.03
13	A	0.0478	12.30	13.52	11.00	69.39	341.85	3.56
13	B	0.0323	12.30	13.52	11.07	103.30	474.14	3.09
13	B	0.0323	12.30	13.52	10.95	102.44	490.29	3.09
13	C	0.0264	12.30	13.52	8.43	130.23	930.88	3.94
13	C	0.0264	12.30	13.52	9.92	141.22	686.31	4.28
13	D	0.0171	12.30	13.52	7.54	156.01	920.22	3.78
13	D	0.0171	12.30	13.52	7.88	159.46	889.08	3.88
13	E	0.0138	12.30	13.52	6.57	171.97	913.42	3.85
13	E	0.0138	12.30	13.52	7.50	183.82	995.97	3.64
14	A	0.0478	4.16	5.03	4.25	43.15	89.19	1.89
14	A	0.0478	4.16	5.03	3.51	39.20	102.89	1.74
14	B	0.0323	4.16	5.03	3.36	56.76	48.46	2.15
14	B	0.0323	4.16	5.03	3.67	59.30	56.11	2.60
14	C	0.0264	4.16	5.03	3.61	85.17	267.76	2.60
14	C	0.0264	4.16	5.03	3.09	78.77	132.42	2.76
14	D	0.0171	4.16	5.03	2.00	80.31	202.04	2.41
14	D	0.0171	4.16	5.03	1.81	76.43	180.44	2.21
14	E	0.0138	4.16	5.03	1.44	80.60	211.70	2.18
14	E	0.0138	4.16	5.03	1.26	75.24	128.40	2.30

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
15	A	0.0478	13.14	12.66	10.68	68.37	253.80	4.01
15	A	0.0478	13.14	12.66	10.29	67.10	347.46	3.80
15	B	0.0323	13.14	12.66	8.83	92.01	220.06	3.39
15	B	0.0323	13.14	12.66	9.47	95.26	223.93	3.55
15	C	0.0264	13.14	12.66	6.71	116.16	344.21	4.53
15	C	0.0264	13.14	12.66	7.16	119.96	362.23	4.07
15	D	0.0171	13.14	12.66	7.02	150.49	498.22	4.16
15	D	0.0171	13.14	12.66	5.57	134.15	461.09	3.97
15	E	0.0138	13.14	12.66	6.48	170.82	883.58	4.48
15	E	0.0138	13.14	12.66	5.58	158.57	373.92	4.39
16	A	0.0478	8.28	9.22	8.85	62.25	94.09	2.64
16	A	0.0478	8.28	9.22	6.16	51.91	101.97	2.41
16	B	0.0323	8.28	9.22	4.88	68.41	84.52	2.57
16	B	0.0323	8.28	9.22	4.90	68.53	96.94	2.69
16	C	0.0264	8.28	9.22	5.38	104.06	229.32	3.79
16	C	0.0264	8.28	9.22	5.44	104.55	174.37	3.39
16	D	0.0171	8.28	9.22	5.69	135.58	408.23	3.60
16	D	0.0171	8.28	9.22	5.16	129.07	328.97	3.28
16	E	0.0138	8.28	9.22	5.24	153.63	621.63	2.86
16	E	0.0138	8.28	9.22	5.49	157.25	427.47	2.92

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}$.$litres^{-1}$ .minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}$.$second^{-1}$)	volume (litres)
17	A	0.0478	11.02	10.34	7.19	56.08	161.94	3.21
17	A	0.0478	11.02	10.34	9.77	65.40	308.91	3.00
17	B	0.0323	11.02	10.34	9.01	92.93	498.85	3.51
17	B	0.0323	11.02	10.34	10.89	102.16	277.76	3.45
17	C	0.0264	11.02	10.34	11.36	151.17	689.46	3.81
17	C	0.0264	11.02	10.34	11.68	153.23	764.76	3.52
17	D	0.0171	11.02	10.34	9.42	174.42	1066.73	3.78
17	D	0.0171	11.02	10.34	10.21	181.52	998.48	3.85
17	E	0.0138	11.02	10.34	7.67	185.83	1091.92	3.94
17	E	0.0138	11.02	10.34	8.36	194.03	1039.82	4.01
18	A	0.0478	9.39	11.83	9.58	64.70	244.20	1.25
18	A	0.0478	9.39	11.83	9.96	66.03	261.69	1.53
18	B	0.0323	9.39	11.83	7.11	82.55	179.77	1.92
18	B	0.0323	9.39	11.83	8.78	91.75	396.79	1.76
18	C	0.0264	9.39	11.83	8.63	131.74	644.09	1.99
18	C	0.0264	9.39	11.83	8.90	133.79	767.10	2.18
18	D	0.0171	9.39	11.83	6.52	145.10	899.18	2.19
18	D	0.0171	9.39	11.83	7.21	152.52	702.52	2.42
18	E	0.0138	9.39	11.83	6.93	176.62	265.78	2.72
18	E	0.0138	9.39	11.83	7.01	177.70	987.02	2.72

APPENDIX C **Clinical Study Data** **(continued)**

subject	resistor	resistivity ($kPa^{0.5}.litres^{-1}$.minute)	measured Maximum Inspiratory Pressure (kPa)	calculated Maximum Inspiratory Pressure (kPa)	peak pressure drop (kPa)	Peak Inspiratory Flow Rate ($litres.minute^{-1}$)	flow acceleration ($litres.minute^{-1}.second^{-1}$)	volume (litres)
19	A	0.0478	2.82	6.44	5.11	47.31	92.84	1.30
19	A	0.0478	2.82	6.44	5.08	47.16	76.24	2.06
19	B	0.0323	2.82	6.44	3.78	60.16	83.70	1.59
19	B	0.0323	2.82	6.44	4.24	63.77	113.31	1.78
19	C	0.0264	2.82	6.44	3.82	87.69	135.23	2.45
19	C	0.0264	2.82	6.44	4.25	92.43	154.51	2.51
19	D	0.0171	2.82	6.44	2.69	93.20	160.78	2.11
19	D	0.0171	2.82	6.44	2.97	97.91	135.03	2.37
19	E	0.0138	2.82	6.44	0.64	53.66	155.49	1.92
19	E	0.0138	2.82	6.44	2.00	94.82	112.89	2.24
20	A	0.0478	12.44	13.79	11.28	70.26	421.20	3.22
20	A	0.0478	12.44	13.79	11.66	71.43	383.12	3.09
20	B	0.0323	12.44	13.79	11.23	103.77	3819.46	4.08
20	B	0.0323	12.44	13.79	10.43	99.98	3305.16	4.69
20	C	0.0264	12.44	13.79	10.23	143.40	2214.06	5.25
20	C	0.0264	12.44	13.79	10.25	143.54	1032.48	5.13
20	D	0.0171	12.44	13.79	9.93	179.01	5859.91	5.29
20	D	0.0171	12.44	13.79	9.13	171.67	6874.86	3.65
20	E	0.0138	12.44	13.79	8.01	189.92	1438.22	5.12
20	E	0.0138	12.44	13.79	8.29	193.25	1415.74	4.80